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NARRATIVE REVIEW

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Hepatitis C in Chronic Kidney Disease: An Overview of the KDIGO Guideline

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Hepatitis C virus (HCV) infection is a global health problem with significant health and economic burden, which can lead to chronic kidney disease (CKD) and affect multiple organ systems. In addition, prevalence of hepatitis C remains higher in patients with CKD, including those on chronic hemodialysis and in individuals with a kidney transplant than in the general population. There has been a dramatic shift in the management of hepatitis C since Kidney Disease: Improving Global Outcome (KDIGO) published its 2008 guideline for the prevention, diagnosis and management of hepatitis C in CKD. As a result, KDIGO published in 2018 an update to this guideline. In this narrative review, we present a synopsis of the guideline, including recommendations for screening and detection of HCV in CKD, treatment of HCV in patients with CKD, treatment of HCV before and after kidney transplantation, prevention of HCV transmission in hemodialysis units, and treatment of kidney disease related to HCV infection. We focus on the clinical aspects of using direct acting antivirals (DAAs) in patients with advanced CKD (G4 and G5), those on dialysis and kidney transplant recipients. We emphasize the importance of carefully managing drug-drug interactions between DAAs and immunosuppressive agents. We discuss timing of HCV treatment before vs. after kidney transplantation. Finally, we highlight areas of uncertainty where further research is needed before any definitive recommendations can be made.

Keywords: Hepatitis C; CKD; Direct Acting Antivirals.

The World Health Organization has called for elimination of viral hepatitis as a public health threat by reducing new infections by 90% and mortality by 65% by 2030.[1] Unlike other communicable diseases, the global burden and relative rank of viral hepatitis increased from 1990 (0.89 million deaths per year) to 2013 (1.45 million deaths per year).[2] Hepatitis B and C cause 96% of mortality related to viral hepatitis. Although deaths from hepatitis B virus (HBV) have plateaued since 1990 after introduction of HBV vaccination, deaths from hepatitis C virus (HCV) continue to rise.[3] HCV remains the most common chronic blood-borne infection worldwide, affecting an estimated 71 million people in 2015.[4] It leads to significant morbidity and mortality because of its hepatic and extrahepatic effects, representing an immense health and economic burden.[5]

Chronic kidney disease (CKD) is defined by Kidney Disease: Improving Global Outcomes (KDIGO) as "abnormalities of kidney structure and function, present for > 3 months, with implications for health,"[6] and is classified based on cause, glomerular filtration rate (GFR) category (G1–G5), and albuminuria category (A1–3), as shown in Figure 1. The current definition of CKD modifies previous classification[7] by emphasizing the cause of kidney disease, adding albuminuria category, and subdividing GFR category 3 in 3a and 3b. CKD has an estimated worldwide prevalence of 8%–16%.[8] According to United States Renal Data System annual data report, CKD prevalence in the US adult general population was 14.8% from 2013 to 2016 and has been stable over the last 2 decades.[9]

Reflecting the complex relationship between HCV infection and CKD, KDIGO has recently published an updated guideline incorporating advances in the prevention, diagnosis, evaluation, and treatment of HCV in this population, which we highlight here.

Detection and Evaluation of Hepatitis C Virus in Chronic Kidney Disease

Relationship Between Hepatitis C Virus and Chronic Kidney Disease

The prevalence of HCV infection in patients undergoing hemodialysis remains higher than in the general population,[10,11] despite a decrease over the last 2

Abbreviations used in this paper: **ALT, alanine aminotransferase; CKD, chronic kidney disease; DAA, direct-acting antivirals; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; GT, genotype; HBV, hepatitis B virus; HCV, hepatitis C virus; KDIGO, Kidney Disease Improving Global Outcomes; KTRs, kidney transplant recipients; MPGN, membranoproliferative glomerulonephritis; NAT, nucleic acid testing; SVR, sustained viral response.**

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GFR categories (mL/min/1.73 m²), description and range			Persistent albuminuria categories, description and range		
			A1	A2	A3
			Normal to mildly increased	Moderately increased	Severely increased
			<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
G1	Normal or high	≥90	Low risk	Moderately increased risk	High risk
G2	Mildly decreased	60–89	Low risk	Moderately increased risk	High risk
G3a	Mildly to moderately decreased	45–59	Moderately increased risk	High risk	Very high risk
G3b	Moderately to severely decreased	30–44	High risk	Very high risk	Very high risk
G4	Severely decreased	15–29	Very high risk	Very high risk	Very high risk
G5	Kidney failure	<15	Very high risk	Very high risk	Very high risk

Figure 1. Current CKD nomenclature used by KDIGO.

decades.[12] Using Dialysis Outcomes and Practice Patterns Study (DOPPS), Jadoul et al[13] reported that in hemodialysis patients, HCV infection defined by a documented diagnosis or antibody seropositivity was present in nearly 10% in 2012–2015. Prevalence ranged from 4% in Belgium to as high as 20% in the Middle East, with intermediate prevalence in China, Japan, Italy, Spain, and Russia.[13] HCV prevalence in US units decreased from 11.5% to 6.9% over 1996–2015 study period. However, given that there were 448,000 patients on hemodialysis in the United States by the end of 2016,[9] this implies that 31,000 of these are seropositive for HCV. Mechanisms of HCV acquisition among hemodialysis patients include typical HCV risk factors (eg, intravenous drug use, remote blood transfusions) and risk of nosocomial transmission during hemodialysis. HCV infection in hemodialysis patients is implicated in diminished quality of life scores and higher risk of hospitalization and mortality.[14] An estimated 4.8% of transplant wait-listed hemodialysis patients are seropositive for hepatitis C.[15] Interestingly, the recent DOPPS study also looked at prevalence of HCV positivity at start of hemodialysis (thus HCV was acquired before hemodialysis), and found a prevalence of approximately 5%, a figure that hardly changed over the last 2 decades, and is much higher than in the general population in the DOPPS countries.[13] The prevalence of HCV infection among kidney transplant recipients (KTRs) is nearly 5% in Western countries,[16] although in France it was lower at 1.4%.[12]

Conversely, HCV infection increases the risk of CKD development and progression.[17,18] Renal deposition of immune complexes (which may or may not be cryoprecipitatable) is the main mechanism of glomerular inflammation caused by HCV infection. Pre-existing comorbidities (eg, hypertension, diabetes, and cardiovascular disease) enhance the rate of progression of CKD to end-stage kidney disease (ESKD) in HCV-positive patients.[19-22] HIV-infected patients who are HCV seropositive have an increased likelihood of a diminished GFR, compared with patients with HIV infection alone.[23] In a retrospective cohort analysis, HCV-positive patients had a 2-fold higher risk of membranoproliferative glomerulonephritis (MPGN) and a 17-fold higher risk of cryoglobulinemia.[18] A direct cytopathic effect of HCV on the kidney is also suspected.[24]

Screening for Hepatitis C Virus in Chronic Kidney Disease and Evaluation of Liver Involvement

All patients with CKD, including those initiating kidney-replacement therapy (hemodialysis, peritoneal dialysis, or transplant evaluation), should undergo screening for HCV. One-time screening needs to be performed by the physician who initially diagnoses CKD, regardless of GFR. Detection of anti-HCV antibody by screening immunoassays (enzyme or chemoluminescence) with infection confirmed by nucleic acid testing (NAT) is required to make a diagnosis. In a recent study of 201 hemodialysis patients in Vietnam, the positive predictive value of anti-HCV antibody for HCV viremia was 73%, whereas the negative predictive value was 90%. In other words, HCV-RNA was positive in 10% of anti-HCV-negative patients.[25] This figure largely results from the window period (delay between viremia

after contamination) and seroconversion (and thus Enzyme-linked Immunosorbent Assay positivity). Thus, in hemodialysis units with a high prevalence of HCV, initial testing with NAT should be considered. NAT samples should be drawn before dialysis, because hemodialysis reduces viremia level. However, this reduction in HCV RNA is not dependent on dialysis schedule or type of membrane used.[26]

Qualitative and quantitative methods are available to confirm HCV viremia with a lower limit of detection of 10–20 IU/mL. HCV antigen tests using core antigens or other protein components have a higher limit of detection (150–3000 IU/mL) and are not commonly used, despite being less expensive.

Serum alanine aminotransferase (ALT) monitoring is an inexpensive way of surveillance for HCV acquisition between regular antibody or NAT testing. Therefore, a baseline serum ALT level, followed by monthly testing, is recommended for patients who initiate in-center hemodialysis or get transferred from another facility. In a prospective study of 2440 hemodialysis patients, a newly elevated ALT level had a sensitivity of 83% and a specificity of 90% for acute HCV infection.[27] Beyond the acute phase, ALT level is generally within normal limits in HCV-positive dialysis patients, even though slightly higher in HCV-positive than HCV-negative patients.[28]

Noninvasive methods (elastography, aspartate aminotransferase platelet ratio index, fibrotest/fibrometer, FIB4 index) are recommended as initial tests for staging liver fibrosis. Transient elastography (fibroscan) measures the velocity of low-frequency elastic shear wave propagation through the liver. This velocity is directly related to tissue stiffness. In a study of 284 Taiwanese hemodialysis patients with chronic HCV, transient elastography was superior to aspartate aminotransferase platelet ratio index in detecting advanced hepatic fibrosis and cirrhosis (Metavir stage F3 and F4).[29] Noninvasive screening tests have a high negative predictive value,[30] but may be false-positive in obese patients, or patients with fluid overload. Nowadays, liver biopsy can be reserved for patients with equivocal noninvasive testing or if an additional diagnosis is possible, such as iron overload.

If cirrhosis is suspected or confirmed, the severity of portal hypertension needs to be determined. Upper endoscopy is indicated to screen for esophageal varices. Clinically significant portal hypertension (hepatic-vein wedge-pressure gradient $\geq$10 mm Hg) is unusual in patients with cirrhosis if elastography is $<$20 kPa and platelet count is $>$150,000/mm^3,[31] and invasive measurement of portal hypertension is only required in the absence of these findings.

Preventing Hepatitis C Virus Transmission in Hemodialysis Units

Measures to prevent HCV transmission in hemodialysis units are well recognized.[32,33] In most reported HCV outbreaks in hemodialysis centers, multiple deficiencies in infection control are typically identified, including lapses in hand hygiene and glove use, injectable medication handling, and environmental surface disinfection. Regular assessment and adherence to evidence-based interventions should be reinforced through observational audits. Guidelines do not recommend isolating HCV-infected patients during hemodialysis sessions. Similarly, use of dedicated dialysis machines for these patients is not recommended because there is no evidence to suggest HCV transmission through internal pathways of single-pass dialysis machines.

Patients in hemodialysis units should be screened for HCV-infection using ALT level monthly and HCV immunoassay or NAT every 6 months. If a newly acquired HCV infection is detected, all patients in the hemodialysis center should be tested and frequency of subsequent testing should be increased, and a detailed review of infection control practices must be conducted. Lastly, seroconversion for HCV suspected to have been acquired on hemodialysis should be reported to public health authorities.

Treatment for Hepatitis C Virus Infection in Patients With Chronic Kidney Disease

Benefits of Treatment

Multiple studies have found an association between sustained viral response (SVR) and reduction in mortality in the general population.[34] In addition to the renal benefits of achieving SVR with treatment of HCV in patients with CKD, additional benefits may include mitigating other extrahepatic manifestations, with reduction in vascular events,[35] and improvement in cryoglobulinemic vasculitis.[36] SVR reduces the risk of deterioration in kidney function and ESKD-related mortality compared with that of untreated patients. In a recent study of 204 liver transplant recipients with HCV, achieving a SVR was associated with 88% lower risk of CKD and 86% lower risk of ESKD (in unadjusted Cox proportional regression analysis).[37]

Therapeutic Options

In addition to low efficacy, interferon-based therapy had limited use in the CKD population because of poor tolerability and concern about graft rejection in KTRs. In addition, ribavirin use in the CKD population is limited by its propensity to cause severe anemia.

NS3/4A protease inhibitors were the first direct-acting antivirals (DAAs) approved in 2011 and since then, numerous DAAs have been licensed. NS5A replication complex inhibitors and nonnucleoside NS5B polymerase inhibitors do not require dose adjustments in advanced stages of CKD and can be used in CKD G4–G5. Sofosbuvir is not recommended for patients with estimated GFR (eGFR) less than 30 mL/min/1.73 m^2.

All treatment candidates should undergo assessment for HBV infection before therapy, and if hepatitis B surface antigen is detected, antiviral therapy for HBV should be considered to prevent HBV reactivation as a consequence of DAA therapy. If initial HBV testing is negative, but there is evidence of prior resolved infection (eg, positive antibody to HBV core antigen), patients should be monitored for HBV reactivation during DAA therapy using serial HBV DNA and liver function tests.

Who Should be Treated?

Given the significant liver, cardiovascular, and kidney benefits of achieving SVR in CKD patients with HCV infection, guidelines recommend that all infected patients should be considered for treatment.

Treatment of Hepatitis C Virus in Patients With Chronic Kidney Disease (G1–G5 and G5D)

Figure 2 shows treatment options for HCV-infected patients with CKD. The joint recommendations from American Association for the Study of Liver Diseases and Infectious Diseases Society of America can be accessed at hcvguidelines.org.[38] For patients with CKD G1–G3b (eGFR >30 mL/min/1.73 m^2), KDIGO[39] and European Association for the Study of the Liver[40] recommend using any one of the available DAAs based on viral load, HCV genotype (GT), degree of fibrosis, and treatment history. No dose modification is necessary for most combination drug regimens. Pangenotypic sofosbuvir-velpatasvir-based regimens were not formally reviewed by the Evidence Review Team at the time of guideline publication. However, the FDA has recently indicated that no dose adjustments are required for these regimens in patients with CKD including those on dialysis. These regimens may be considered pending their availability in various jurisdictions. Sofosbuvir is predominantly renally cleared (80%) and is approved for use only in individuals with eGFR >30 mL/min/1.73 m^2. These patients typically receive a combination of sofosbuvir-velpatasvir, ledipasvir-sofosbuvir, glecaprevir-pibrentasvir, or grazoprevir-elbasvir. Use of protease-inhibitors is contraindicated in patients with cirrhosis because of reports of hepatic decompensation with these agents.

In CKD G4–G5, including patients on dialysis (G5D), a low eGFR, in addition to viral GT, is the major determinant in choice of DAAs. A regimen combining elbasvir and grazoprevir has been studied in advanced CKD and is recommended for use in HCV GT1 and GT4. In the C-SURFER trial, HCV GT1-infected patients with CKD G4–G5 were treated with a combination of elbasvir and grazoprevir for 12 weeks. Both drugs are metabolized by CYP3A4 and are primarily (>90%) excreted in feces with <1% renal elimination, making dose adjustment unnecessary. SVR was 99% with excellent tolerability. Change in eGFR and need to initiate hemodialysis was similar in intervention and control groups.[41,42] Coadministration with CYP3A4 inducers (eg, rifampin, phenytoin, St. John's wart) is contraindicated because it may reduce antiviral activity of both agents. Coadministration with drugs that inhibit OATP1B1/3 (enalapril, statins, digoxin, and some angiotensin-receptor blockers) may increase levels of grazoprevir and cause hyperbilirubinemia. Similar to other protease-inhibitors, grazoprevir cannot be used in patients with Child-Turcotte-Pugh class B and C cirrhosis because of risk of hepatotoxicity. Caution is advised when using concomitantly with drugs that are extensively metabolized in liver and have narrow therapeutic index (eg, cyclosporine). Viral eradication may improve hepatic metabolic function, thus leading to decreased levels and efficacy of such drugs.

Pangenotypic glecaprevir-pibrentasvir combination is an option for the treatment of HCV in CKD G4–G5D patients, regardless of GT. It can be used in patients with cirrhosis and those who failed treatment with interferon-

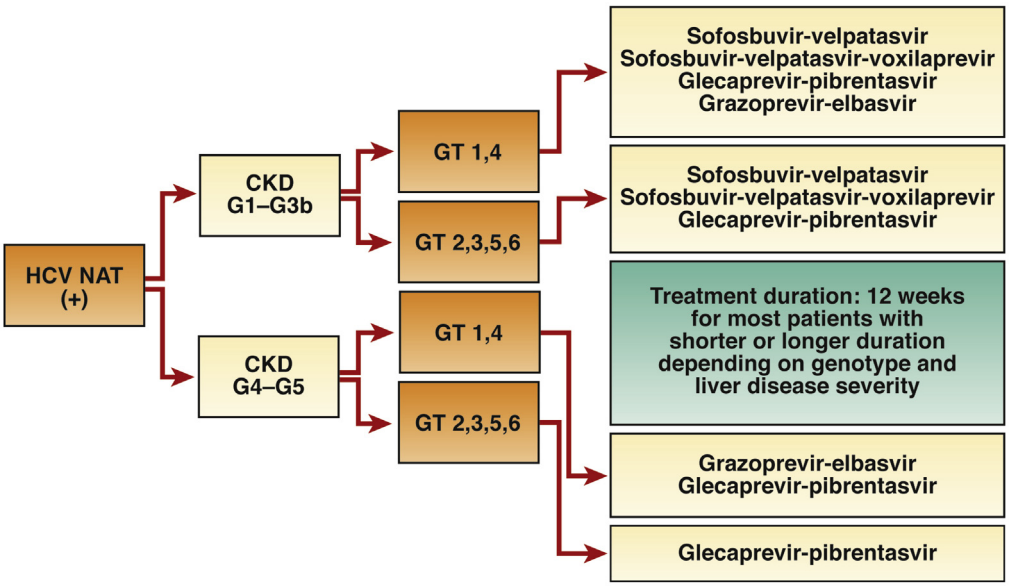

Figure 2. Treatment scheme for HCV-infected patients with CKD (G1–G5).

based therapies. In the EXPEDITION-4 study, the glecaprevir-pibrentasvir regimen was used for 12 weeks to treat HCV GT1–GT6 in patients with CKD G4–G5 and achieved SVR of 98% (102 out of 104 patients).[43] Most (82%) patients were on hemodialysis and 42% had been treated previously, including 2 with sofosbuvir-based therapy. In an integrated analysis of 9 trials with 2041 patients without cirrhosis, treatment with glecaprevir-pibrentasvir for 8 weeks achieved a similar SVR (98%) and was efficacious regardless of baseline kidney function.[44] Because these drugs are highly protein bound, timing of administration does not need to be altered even on dialysis days.

RUBY-II enrolled patients with CKD G4–G5D with HCV GT1a and GT4 infection and treated them with ritonavir-boosted paritaprevir and ombitasvir (plus dasabuvir in GT1a patients [PrOD regimen]) for 12 weeks. Of the 18 treated patients, 17 achieved SVR and the remaining 1 patient elected to undergo kidney transplantation.[45] Trials of DAAs in patients with advanced CKD are summarized in Table 1.

Screening for hepatocellular carcinoma is recommended for patients with cirrhosis after achieving SVR, and may also be considered for patients with stage 3 fibrosis.

Treatment of Hepatitis C Virus in Kidney Transplant Recipients

Although published data in KTRs are less abundant, results are as satisfactory as in liver transplant recipients. KTRs, even with well-functioning grafts, have baseline CKD (because of various immunologic and nonimmunologic mechanisms), which is classified as G1T–G5T. Similar to patients with CKD, KTRs with a GFR >30 mL/min/1.73 m^2 (CKD G1T–G3bT) and HCV GT1 and GT4 can be treated with either a sofosbuvir-based regimen or pibrentasvir-glecaprevir. For GTs 2, 3, 5, and 6, pibrentasvir-glecaprevir is recommended. If eGFR is <30 mL/min/1.73 m^2, the same regimens are recommended as used for CKD G4–G5D.

Interferon-free regimens are recommended for KTRs. DAAs, including sofosbuvir-based regimens, are well-tolerated and effective, but do require dose-adjustment of immunosuppressive medications in more than half of KTRs.[46] Ledipasvir-sofosbuvir use in 114 KTRs with eGFR >40 mL/min/1.73 m^2 for 12 or 24 weeks showed 100% SVR regardless of treatment duration. Serious adverse events occurred in 11%, with 3 patients experiencing an increase in creatinine.[47] MAGELLAN-2 was a phase 3 open-label trial that used glecaprevir-pibrentasvir for 12 weeks in 80 liver transplant recipients and 20 KTRs infected with HCV GTs 1–6 and reported SVR of 98%. There was 1 virologic failure and 1 patient dropped out because of adverse events.[48]

Drug-drug interactions are an important consideration in KTRs and DAAs can lead to elevated or suppressed levels of immunosuppressive medications, resulting in graft rejection or toxicity. Cyclosporine, tacrolimus, everolimus, and sirolimus are metabolized by cytochrome P-450. Protease-inhibitors are associated with a significant risk of interaction with calcineurin inhibitors or mTOR inhibitors, whereas NS5A inhibitors (ledipasvir, daclatasvir) and NS5B inhibitors (sofosbuvir)

Table 1. Comparison of Trials Reporting Use of DAAs in Advanced CKD (G4 and G5)[a]

Study	C-SURFER[44]	EXPEDITION-4[46]	RUBY-II[48]
Design	Multicenter randomized, double-blinded phase 3 trial	Multicenter, open label, single-group, phase 3 trial	Multicenter, open-label, phase 3 trial
No. of patients	235	104	18
Treatment naive, %	80	58	72
Patients on dialysis, %	76	82	94
Patients with cirrhosis, %	6	19	0
HCV genotypes	GT1	All GTs, GT1 (52%)	GT1a (72%), GT4
Intervention	Immediate treatment with EBR/GZR	Glecaprevir/pibrentasvir	OBV/PTV/r ± DSV (for GT1)
Comparison	Deferred treatment group	None	None
Duration of treatment, *wk*	12	12	12
Follow-up	16 wk post-treatment	36 weeks post-treatment	24 weeks post-treatment
SVR-12, %	99	98	94
ITT analysis	Yes	Yes	Yes
Rate of relapse	1 patient	None	Not reported
Frequency of adverse events	Similar in both groups	Serious adverse events in 24% of patients	Serious adverse events in 5% of patients
Decline in kidney function	2 patients initiated HD, 4 patients had a negative change in CKD stage	No significant change in mean eGFR	17 out of 18 patients were on dialysis at the start of study
Discontinued treatment because of adverse events	None	4 patients	2 patients

CKD, chronic kidney disease; DAA, direct-acting antivirals; DSV, dasabuvir; EBR/GZR, elbasvir/grazoprevir; eGFR, estimated glomerular filtration rate; GT, genotype; HCV, hepatitis C virus; HD, hemodialysis; ITT, intention to treat; OBV, ombitasvir; PTV/r, ritonavir-boosted paritaprevir; SVR-12, sustained viral remission at 12 weeks.

[a]eGFR <30 mL/min/1.73 m^2. See Figure 1 for nomenclature.

are associated with a lower risk of interaction with these agents. Concurrent use of elbasvir-grazoprevir with cyclosporine is not recommended because it increases area under the curve for grazoprevir by 15-fold and elbasvir by 2-fold. Elbasvir-grazoprevir results in an increase in tacrolimus level by 43%, so level needs to be closely monitored. Other protease inhibitors, such as simeprivir and paritaprevir, have similar interactions. Protease inhibitors do not interact with mycophenolate mofetil. Drug-drug interactions should be checked using a reliable source before initiating therapy, such as The University of Liverpool Web site.[49]

Management of Patients With Hepatitis C Virus Before and After Kidney Transplantation

Figure 3 depicts management options for HCV in kidney transplant candidates.

Hepatitis C Virus–Positive Recipient

Kidney transplantation remains the best treatment option for patients with ESKD because of a significant survival advantage,[50,51] regardless of HCV status. Although patient and graft survival is inferior in patients with persistent HCV replication after transplant compared with HCV-negative recipients,[52] patient survival is better compared with remaining on dialysis.[53] HCV-infected patients with decompensated cirrhosis should be evaluated for combined liver-kidney transplantation.

Since the advent of DAAs, HCV infection in potential KTRs can be treated before or after kidney transplantation. Timing of HCV treatment depends on donor-type, wait-list times, center-specific policies regarding the use HCV-infected deceased donors, HCV GT, and severity of liver fibrosis. If a living kidney transplantation is anticipated without a long wait, HCV treatment can be deferred until after transplantation. However, wait-times longer than 24 weeks allow sufficient time for treatment (12 weeks) and confirmation of SVR (12 weeks).

For deceased donors, KDIGO strongly recommends that kidneys from HCV NAT-positive donors should be directed to recipients with positive NAT.[39] Thus, if acceptance of a graft from an HCV-positive donor reduces the wait-time for transplantation, a patient can undergo transplantation with an HCV-positive kidney and get treatment for HCV-infection after transplant. The patient needs to provide informed consent for this approach. In a multicenter study, this strategy did not adversely affect patient or graft survival.[54] Wait-list times vary according to the region but are typically shorter for recipients of HCV-positive organs. Treatment of HCV in KTRs can be initiated once patient is on a stable immunosuppression regimen. Deferred treatment may not be suitable for patients with more advanced liver fibrosis. However, with the availability of DAAs, compensated cirrhosis is no longer a contraindication for an isolated kidney graft, because DAA therapy halts and eventually, to some extent, even reverses the liver disease. Also, because of potential for drug-drug interactions with immunosuppressive medications, unpredictable timing of kidney transplantation, and poor prognosis of patients with HCV and CKD, many clinicians are inclined toward treating these patients as soon as possible.

Hepatitis C Virus–Positive Donor

HCV NAT-positive living donors should be treated and SVR should be confirmed before transplantation, as long as they meet other criteria for a suitable living donor and have no evidence of cirrhosis. In the United States, almost 100,000 patients are wait-listed for kidney transplantation each year[55] and waiting times exceed 3–5 years.[56] Despite the substantial need for organs, more than 800 kidneys from HCV-infected

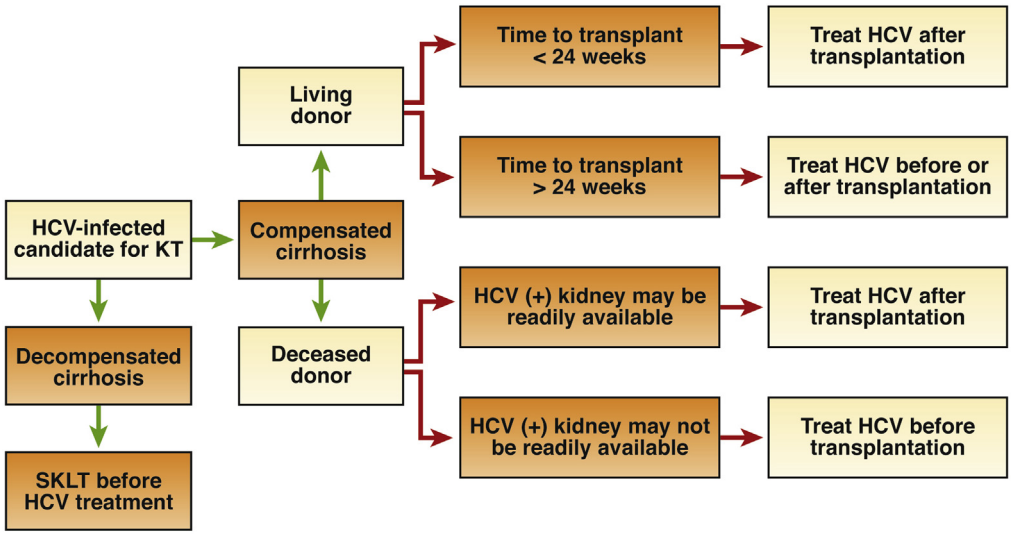

Figure 3. Proposed scheme for HCV treatment in kidney transplant candidates. KT, kidney transplant; SKLT, simultaneous liver kidney transplant.

donors were discarded in 2016.[56] Overall 4.2% of organs are offered from HCV-positive donors.[57] If a donor is anti-HCV-positive but NAT-negative, the kidney can be safely transplanted into an HCV-negative recipient.[57] Results of kidney transplantation from HCV NAT-positive donor to HCV-positive recipients who were treated with DAAs following transplantation are also reassuring.[58] However, whether these kidneys can be routinely transplanted in HCV-negative recipients is still under investigation. An analysis of the US Organ Procurement and Transplantation Network database through 2012 showed inferior outcomes in HCV-negative recipients who received HCV-positive kidneys[59] and this practice was considered unacceptable. However, the availability of DAAs has led clinicians to reconsider this. In the THINKER-1 trial, all of the 10 HCV-negative patients who received HCV-positive kidneys followed by DAA treatment achieved HCV cure and excellent kidney function.[60] In EXPANDER-1, 8 HCV-negative patients were transplanted with HCV-positive kidneys and were treated with 1 dose of grazoprevir/elbasvir pretransplant and then daily for 12 weeks post-transplant. HCV RNA was detected in 4 patients on postoperative day 1 but was not detected later. HCV RNA was never detected in the other 4 recipients.[61] However, until more data are available, this approach is considered investigational.

Choice of Immunosuppression

As immunosuppression facilitates viral replication, viral load increases after transplantation and there is increased risk of death from infection in the first 6 months after transplantation.[62] The increased risk of death from antibody induction drops after the first 6 months[62] and studies have suggested that antibody induction has no detrimental effect on long-term survival in HCV-positive patients.[63] Steroid-sparing regimens may reduce the risk of post-transplant diabetes[64] but there is no effect on mortality.[63] Tacrolimus also increases the risk of diabetes[65] and mycophenolate mofetil has shown to increase serum HCV RNA concentration.[66] However, both these drugs are the backbone of current immunosuppression protocols and mycophenolate mofetil can be used regardless of HCV status.[62] No single induction or maintenance immunosuppression medication is contraindicated in KTRs with HCV.

Follow-up

HCV-infected KTRs who are treated before transplantation and achieve SVR should be tested by NAT 3 months after transplantation. HCV-infected KTRs should be tested for proteinuria every 6 months and development of proteinuria (urine protein to creatinine ratio >1 g/g or 24-hour urine protein >1 g on 2 occasions) should trigger a kidney biopsy.

Diagnosis and Management of Kidney Diseases Associated With Hepatitis C Virus Infection

Although chronic HCV can cause tubulointerstitial injury,[67] the most frequent form of renal involvement is MPGN, often caused by cryoglobulinemic vasculitis. MPGN can also present in the absence of cryoglobulinemia.[68,69] Membranous nephropathy is another less frequent histologic pattern in patients with HCV infection.[70] Clinical manifestations include proteinuria, microscopic hematuria, hypertension, and acute nephritic and nephrotic syndrome. Kidney biopsy can establish a precise diagnosis and exclude other etiologies, such as diabetic nephropathy, not infrequent in patients with HCV.[71] Patients with HCV-associated glomerular disease with stable kidney function and nonnephrotic range proteinuria should initially be treated with DAAs because this can result in remission of hematuria, proteinuria with improvement in eGFR.[72] In patients with rapidly progressive kidney failure, acute cryoglobulinemic flare, or nephrotic syndrome, immunosuppression (using rituximab as first-line agent) with or without plasma exchange should be considered before initiating DAAs. The superiority of rituximab over conventional immunosuppressants in cryoglobulinemic vasculitis was established in 2 randomized trials,[73,74] but these trials included a minority of patients with renal involvement. In a recent prospective study with 6-year follow-up, rituximab use in 16 patients with diffuse MPGN was associated with an improvement in nephropathy starting the second month after rituximab administration.[75] Rituximab can lead to reactivation of HBV, and a black box warning on the rituximab label has been added by the Food and Drug Administration.[76]

Areas of Uncertainty

The role of DAAs in preventing and slowing the progression of CKD in the HCV-infected population is not clear and needs to be evaluated. Optimal timing of antiviral therapy before or after kidney transplantation in kidney transplant candidates needs to be clarified and use of HCV-positive donors for HCV-negative recipients (with DAAs) needs to be explored further. Additional studies are required to understand how meticulous attention to body fluid precautions can be improved further to prevent HCV transmission within hemodialysis units, thus obviating isolation or dedicated dialysis machines for HCV-infected patients.

Conclusions

Significant strides have been made in the treatment of HCV-infection since the availability of DAAs. Especially, pangenotypic medications that can be used even in

patients with advanced CKD have made HCV cure a realistic goal. However, financial concerns[77] and lack of referral to hepatologists[78] for treatment remain significant obstacles toward complete elimination of HCV. Promoting access to DAAs[79] and reducing risk of HCV transmission in dialysis centers, along with universal immunization for HBV, can make it possible to eliminate viral hepatitis within the next decade as a global health problem.[80]

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Conflicts of interest
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