



REVIEW ARTICLE

Hepatitis C Virus Infection and Renal Disorders

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Abstract

Hepatitis C virus (HCV) infection is frequently associated with extrahepatic disorders, among which renal diseases are frequent. This article highlights the most frequent HCV-associated renal disorders, the impact of HCV infection on chronic renal disease and renal transplantation, and the role of current direct-acting antiviral therapies. HCV is associated with membranoproliferative glomerulonephritis, acceleration of end-stage renal diseases in patients with glomerulopathies, and a higher risk of death in patients affected by chronic kidney disease. Before the introduction of direct-acting antiviral drugs as treatment modality, renal transplantation was a challenging clinical problem because the drugs available until 2011 obtained a poor sustained virologic response, had several side effects, and caused acute rejection when used after transplantation. The knowledge of the viral structure and its replication allowed the discovery of new classes of direct-acting antiviral drugs that revolutionized this scenario. These new drugs are comparatively more effective and safer. Accumulating evidence suggests that it is possible to cure HCV-related glomerulonephritis, and obtain a sustained virologic response in patients with renal failure, or on dialysis, before commencing transplantation. Finally, it became possible to transplant HCV-positive kidneys into HCV-positive or HCV-negative recipients.

Keywords: direct antiviral agents; extrahepatic disorders; hepatitis C virus; membranoproliferative glomerulonephritis; mixed cryoglobulinemia

Received: 12 November 2018; *Accepted after Revision:* 20 December 2018; *Published:* 16 January 2019

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How to cite: Salvadori M, Tsalouchos A. Hepatitis C virus infection and renal disorders. *J Ren Hepat Disord.* 2019;3(1):1–14.

Doi: <http://dx.doi.org/10.15586/jrenhep.2019.43>

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Introduction

Hepatitis C virus (HCV) infection is a relevant health issue with 150–170 million people chronically infected worldwide (1). These patients are at high risk of developing liver complications such as cirrhosis and liver cancer. A large proportion of patients with HCV infection are also affected by extrahepatic complications (2–5), as summarized in Table 1. Some of these clinical conditions are common, while others are anecdotal or infrequently reported (2–5).

This article provides an overview of renal disorders associated with HCV infection, their main characteristics, and therapy, with emphasis on direct-acting antiviral (DAA) therapies.

HCV epidemiology in patients affected by renal diseases

The prevalence of HCV infection in the general population is estimated to be approximately 3% (6). In dialysis patients, the prevalence is higher, and the Dialysis Outcomes and

Table 1. The major extrahepatic manifestations in patients with hepatitis C virus infection

Immune-related extrahepatic manifestations
- Mixed cryoglobulinemia
- Cryoglobulinemic vasculitis
- B-cell NHL
- Sicca syndrome
- Arthralgia/myalgia
- Autoantibody production (cryoglobulins, rheumatoid factor, anticardiolipin, etc.)
- Polyarteritis nodosa
- Monoclonal gammopathies
- Immune thrombocytopenia
Inflammatory-related extrahepatic manifestations
- Type 2 diabetes mellitus
- Insulin resistance
- Glomerulonephritis
- Renal insufficiency
- Fatigue
- Cognitive impairment
- Depression
- Impaired quality of life
- Polyarthritits/fibromyalgia
- Cardiovascular disorders (i.e. stroke and ischemic heart disease)

NHL, Non Hodgkin Lymphoma.

Practice Patterns Study (DOPPS) reported prevalence rates ranging from 2.6% to 22.9% (7). Excluding dialysis patients, HCV prevalence is higher in patients with kidney diseases with respect to general population. HCV may cause chronic kidney disease (CKD) via specific forms of glomerulonephritis (GN), primarily membranoproliferative GN (MPGN) which is associated with mixed cryoglobulinemia (MC). In such cases, MC represents HCV/anti-HCV immune complex in association with rheumatoid factor (RF) and complement (8). Epidemiological studies conducted in the United States (NHANES II) and Taiwan, where HCV infection is endemic, have documented the interaction and relationship between HCV infection and CKD (9, 10). The expression by renal parenchyma of CD81 and SRB1 receptor facilitates the binding of HCV to the renal cell surface and its endocytosis (11). Consequently, HCV-RNA and the related proteins have

been found in the mesangial, tubular, epithelial, and endothelial cells of the kidney (12, 13). HCV-associated renal injury may also be facilitated by the presence of toll-like receptors (TLRs) on renal cells. TLRs are able to recognize molecules associated with microbial pathogens and, once activated, may induce an immunological response (14). The increased expression of TLR3 on renal cells, observed in renal biopsy samples, may justify a link between TLR3 and HCV-related glomerular diseases.

HCV and CKD

HCV infection is frequently associated with CKD stages 4 and 5. Blood transfusions and nosocomial transmission in dialysis patients are the causes of the higher prevalence of HCV infection in these patients when compared with the general population. In patients on dialysis, the nosocomial transmission also seems to occur independently of blood transfusions (15–17). In one study, of the 1423 hemodialysis patients who never received previous blood transfusions, 18% had hepatitis C antibodies (15). In addition to a higher frequency, epidemiological studies have demonstrated that HCV infection is an independent risk factor not only for the development of CKD, but also for the rapid progression of CKD (ERCHIVES study) (18). Another study (19) confirmed that HCV-positive patients have a 40% higher chance of developing renal failure compared to HCV-negative patients. These findings were further confirmed by a systematic review and meta-analysis (20). In addition to being a risk factor for renal failure, HCV infection is also a risk factor for mortality in patients with end-stage renal disease (ESRD). A meta-analysis of 14 observational studies confirmed that HCV-Ab-positive serological status is an independent and significant risk factor for death in patients on dialysis (21). Similarly, a prospective observational study of 16,720 hemodialysis patients found that HCV positivity is associated with an increased risk of mortality (RR 1.17) (22). The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL) HCV study is a large prospective community-based cohort study in Taiwan that provides an excellent opportunity to investigate the natural history of HCV infection and associated diseases (23). Recently, a study by Lai et al. (24) demonstrated that chronic HCV infection is an independent risk factor for the development of ESRD in patients with genotype 1. Patients with low and high HCV-RNA levels had, respectively, 2.6- and 4.3-fold increased risk of developing ESRD compared with patients who were not infected with HCV (Figure 1). In a further study, Lai et al. demonstrated that, in addition to viral load, genotype 2 is a strong predictor of CKD (25). The mechanism by which HCV infection increases the risk of morbidity and mortality in patients with CKD is not clear. About 50% of the deaths are related to cardiovascular diseases, and an association between malnutrition-inflammation syndrome (MIA syndrome) and poor

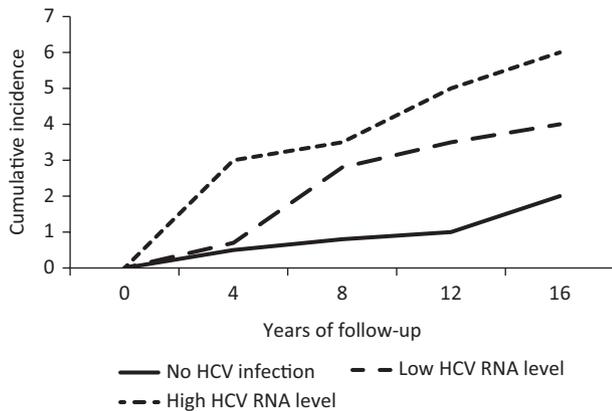


Figure 1. Cumulative risk of end-stage renal disease in patients affected by genotype 1 (24).

outcomes has been suggested (26). Other studies have highlighted that HCV has an atherogenic role, which could aggravate metabolic syndrome (27).

HCV-associated renal diseases

HCV-related renal damage comprises several clinicopathological aspects that include glomerular and/or interstitial lesions (28–30) as summarized in Table 2. MPGN is the typical and most frequent pathologic entity. Kidney involvement may be the result of two different processes: the immune-mediated tissue damage or HCV-mediated direct injury. In addition, environmental or host factors, genetic background, decompensated cirrhosis, and diabetes may contribute to renal damage in the setting of HCV infection. The HCV lymphotropism represents the main pathogenetic mechanism of HCV-related clinical manifestations. The HCV antigen is responsible for both T-lymphocyte and B-lymphocyte activation, leading to

the production of autoantibodies and immune complexes involved in the pathogenesis of HCV-related nephropathy (31). In addition, the virus *per se* may directly induce tissue damage by infecting the endothelial, tubular, and epithelial cells, and infiltrating leukocytes. A high prevalence of occult HCV infection in patients with primary and secondary glomerular nephropathies (32, 33) and the presence of HCV antigen in kidney tissue of patients with various glomerulopathies (34) support the hypothesis of direct injury mediated by HCV.

Mixed cryoglobulins and MPGN

Among the HCV-related extrahepatic manifestations, cryoglobulinemic vasculitis represents a severe condition often complicated by renal involvement (30). According to the type of immunoglobulins (Igs) involved, cryoglobulins (CGs) have been classified into type I, type II, and type III (35). Type I CG is frequently seen in monoclonal gammopathies like multiple myeloma or Waldenstrom’s macroglobulinemia. Types II and III CGs are a mix of both polyclonal IgG and monoclonal IgM with RF activity. Type II CG is mainly found secondary to infections such as HCV, hepatitis B virus (HBV), and human immunodeficiency virus. Type III CG is frequently associated with connective tissue diseases and rarely found in HCV-related MPGN. Mixed cryoglobulins (MCs) are the typical consequence of HCV infection and are often associated with MPGN. Types II and III MCs are generally present. A polyclonal IgG binds to another immunoglobulin, which acts as an antiglobulin and as an anti-IgG RF. HCV is known to be the cause of 80% of MCs. The pathophysiological mechanism of HCV-related GN probably involves E2-CD81 interaction. The E2 protein of HCV interacts with the CD81 that is the cellular receptor for HCV and is required for the infection of hepatocytes (36). Type I MPGN is the most frequent GN associated with chronic

Table 2. Histopathological features of hepatitis C virus-related renal involvement

Renal disease pattern	Histologic features	Frequency
Diffuse or focal MPGN	Mesangial cells proliferation plus deposits of immune complexes	Typically found
Mesangial proliferative GN	Diffuse mild mesangial matrix expansion and mesangial cells proliferation	Occasionally found
Tubulointerstitial nephritis	Interstitial fibrosis with negative immunofluorescence	Rare
Membranous GN	Subepithelial deposits of immune complexes	Occasionally found
IgA nephropathy	Mesangial IgA deposits	Rare
Focal segmental glomerulosclerosis	Sclerosed glomeruli and tubular atrophy, negative immunofluorescence	Rare
Immunotactoid glomerulopathy and fibrillary GN	Extracellular deposits of microfibrils; IgG and C3 immunofluorescence	Rare

MPGN, membranoproliferative GN; GN, glomerulonephritis.

HCV infection. The pathogenesis of MPGN is due to glomerular deposition of immune complexes often containing MCs; however, glomerular deposition of immune complexes in HCV-MPGN may be observed even in the absence of MCs (37). The immune complex deposits in the mesangium and subendothelium activate the complement system and mononuclear cells, which alter glomerular permeability and cause subsequent cell damage through the release of proteases and oxidants (38). Overall, the prevalence of MPGN is higher in HCV patients with MCs. HCV-RNA has been observed in 80% of patients with cryoglobulinemia-associated MPGN, but only in 25% of MPGN patients without cryoglobulinemia (38). MPGN may be associated with HCV infection independently of circulating MCs. In such cases, the immunocomplexes containing HCV are responsible for the GN. Viral nonstructural protein 3 (NS3) may be present in the deposits with a linear or granular pattern along the capillary walls and the mesangium (33).

Membranous Nephropathy

Several cases of membranous nephropathy (MN) have been described in HCV-infected patients (39, 40). The findings are similar to those observed in the classic idiopathic MN due to phospholipase A2 receptor (PLA2R). Complement level in the serum is normal and both CGs and RF are absent. Yamabe et al. (40) found that 8% of MN patients were HCV-positive compared to less than 1% of patients with different forms of GN with the exclusion of MPGN.

Other glomerulonephritis

Diffuse proliferative GN with paramesangial dense IgM and C3 deposits may be occasionally observed in HCV-positive patients (41). The association of IgA nephropathy with HCV infection has been reported (42–44). Some of these reports describe a successful treatment with interferon alpha (IFN α). Several studies have highlighted the association between HCV and focal segmental glomerulosclerosis (FSGS) (45, 46). Shah et al. (46) reported that treatment with pegylated IFN α resulted in a sustained virologic response (SVR), with a clinical remission lasting more than 5 years. Six cases of fibrillary immunotactoid glomerulopathies associated with HCV infection have been described (47–49). The best described are six cases by Markowitz et al. (47). They describe four cases of fibrillary GN and two cases of immunotactoid glomerulopathy associated with HCV infection. The renal biopsy showed a membranoproliferative pattern, but electron microscopy revealed fibrils of 16–28 nm diameter in fibrillary GN and 35–45 nm in immunotactoid glomerulopathy. Both fibrillary GN and immunotactoid glomerulopathy are similar to cryoglobulinemic GN, suggesting a common pathogenetic mechanism of organized glomerular deposits. In a review article, Johnson et al. (50) observed that patients affected by MPGN in association

with HCV infection often have tubulointerstitial inflammation and scarring. More recently, in another study (51), tubulointerstitial changes were frequently observed in HCV-infected patients, and the viral antigens and HCV-RNA were detected in the tubulointerstitium of these patients.

Kidney transplantation and HCV infection

The pre-transplant prevalence of HCV infection has been reported to be as high as 40% (52). In recent reports, the prevalence is lower due to the prophylactic measures adopted in CKD patients but still ranges from 3% to 80% (53). The survival of HCV-positive RNA-positive kidney transplant recipients is poor, but higher with respect to HCV-positive RNA-positive patients who remain on dialysis (54–56); however, the survival rates in CKD and renal transplant patients have markedly improved after the introduction of the DAA therapies. The most frequently reported HCV-related adverse events after kidney transplantation are acute and chronic graft dysfunction, infections, posttransplant diabetes mellitus (PTDM), posttransplant lymphoproliferative disease, and GN (57). Cosio et al. (58) documented a high risk of acute transplant glomerulopathy and acute vascular rejection in HCV-positive recipients. An increased risk of chronic transplant glomerulopathy was documented in a meta-analysis of eight clinical trials (59) and in another large single-center study (60). A higher incidence of infections in HCV transplanted patients is debated, but a Spanish study with 1302 kidney transplant patients documented a higher incidence of bacteremia and upper urinary infections (61). HCV infection is an independent risk factor for PTDM (62, 63). Virus-induced pancreatic β -cell dysfunction has been proposed as the pathogenetic mechanism (64). An increase in posttransplant lymphoproliferative disorders has been described in HCV patients transplanted with kidney or other organs (65). Both recurrent and *de novo* GN have been observed in HCV renal transplant patients. HCV-associated MPGN and MN recur after transplantation (66). The recurrence is more frequent after the second year and the incidence rate ranges from 20% to 30% for MPGN and from 3% to 7% for MN (67), similar to native kidney disease. HCV is also a risk factor for development of *de novo* GN. One study reported an incidence rate as high as 63% for *de novo* GN (68). Similar findings were reported by others (69). *De novo* FSGS has also been reported in HCV renal transplant patients and a direct pathogenesis by HCV on podocyte has been suggested in such patients (11).

Treatment

The introduction of DAA drugs has remarkably ameliorated virus-mediated pathological changes in renal transplant patients. Relevant effects of these drugs are discussed in this section.

History of HCV therapy

HCV is an enveloped virus with single stranded RNA and a genome composed of structural and nonstructural proteins (Figure 2) (6). Seven genotypes have been identified and divided into subtypes and strains (70). The genotypes are differentially distributed worldwide and the efficacy of DAA drugs may vary according to the HCV genotype. In the past, interferon-based regimen constituted the standard of care treatment. The first drug used was the recombinant alpha interferon (IFN α) in combination with ribavirin. Initially, IFN α was used as monotherapy, but the efficacy in terms of SVR was poor, the treatment was expensive, and several side effects were reported. In addition, when used in transplant patients, it could generate severe acute rejection (71). On the other hand, when used in combination with ribavirin, the treatment leads

to dose-dependent hemolytic anemia (72). Fabrizi et al. (73) performed a meta-analysis and concluded that the efficacy and safety of IFN-based therapies are unsatisfactory with low efficacy and high rate of side effects, particularly when used in transplant patients. This treatment was the standard of care until 1998. Later, the introduction of pegylated-IFN α increased the SVR and it became the standard of care until 2011.

The knowledge of the mechanism of action of HCV and the viral proteins involved in its replication allowed for the development of specific drugs for direct antiviral (DAA) treatment. The first generation of DAA was represented by boceprevir and telaprevir, which inhibit the NS3/4A protease activity. However, these drugs frequently induced viral resistance and therefore are combined with pegIFN and ribavirin. There are four classes of DAA agents based on their mechanisms of action (Table 3).

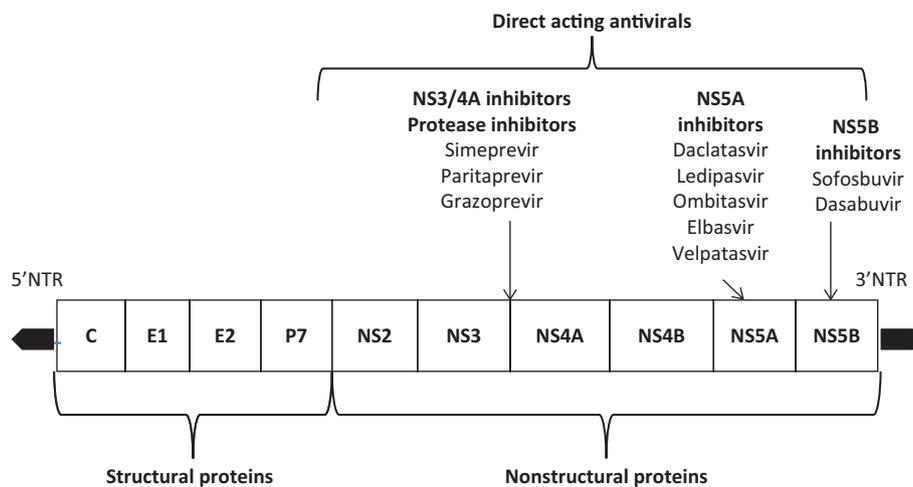


Figure 2. The hepatitis C virus genome and target sites of action of the direct-acting antiviral agents (6).

Table 3. The four classes of direct-acting antiviral agents

The four classes of DAAs	Mechanism of action	Drugs (targeted genotypes in brackets)
NS3/4A PIs	Block a viral enzyme (protease) that enables the HCV to survive and replicates in the host cells	Simeprevir (1, 4) Paritaprevir (1, 4) Grazoprevir (1, 3, 4)
Nucleoside and nucleotide NS5B polymerase inhibitors	Target the HCV to stop replicating itself in the liver	Sofosbuvir (1-4)
NS5A inhibitors	Block a virus protein, NS5A, that HCV needs to replicate	Ombitasvir (1, 4) Pibrentasvir (1-6) Daclatasvir (3) Elbasvir (1, 4) Ledipasvir (1) Ombitasvir (1) Velpatasvir (1-6)
Non-nucleoside NS5B polymerase inhibitors	Stop HCV from reproducing by inserting themselves into the virus so that other pieces of HCV cannot attach to it	Dasabuvir (1)

DAAs, direct-acting antivirals; HCV, hepatitis C virus.

The first class includes the protease inhibitors (PIs) acting on NS3/4A. These drugs block a viral enzyme (protease) that enables the HCV to survive and replicate in host cells. The best-known drugs of this class are simeprevir and paritaprevir acting on genotypes 1 and 4, and grazoprevir acting on genotypes 1, 3, and 4. These drugs are usually used in combination to achieve a stable SVR (74). The second class comprises nucleoside and nucleotide NS5B polymerase inhibitors that inhibit intrahepatic replication. The main drug belonging to this class is sofosbuvir. Sofosbuvir acts against genotypes 1–4 and was recently approved for use in combination with other DAAs. In particular, sofosbuvir has been studied in the HCV-TARGET study (75). As an increased rate of adverse events was observed in patients with renal failure, the current guidelines of the American Association for the Study of Liver Disease (AASLD) recommend that sofosbuvir should be used only in patients with an estimated glomerular filtration rate (eGFR) higher than 30 mL/min (74). The third class includes the NS5A inhibitors that block the virus protein NS5A, which is required for replication and various stages of infection. Several drugs belong to this class, which include ombitasvir (acting against genotypes 1 and 4), pibrentasvir (a pangenotype drug), daclatasvir (acting on genotype 3), elbasvir (acting on genotypes 1 and 4), ledipasvir (acting on genotype 1), and velpatasvir (a pan-genotype drug). A combination of ombitasvir/paritaprevir-ritonavir and dasabuvir is often used and represents the 3D regimen, marketed as Viekira Pak. This combination has been studied in the RUBY-I trial in CKD patients (76) obtaining a SVR without side effects. The fourth class of drugs includes dasabuvir, a non-nucleoside NS5B polymerase inhibitor that stops HCV from reproducing by inserting itself into the virus so that other pieces of the HCV cannot attach to it. All the currently recommended regimens include at least two agents of different classes. The most common combination is a NS5A inhibitor with a polymerase inhibitor or a protease inhibitor. For resistant populations, the addition of ribavirin is recommended (77).

Treatment of HCV-related cryoglobulinemic GN

In the days of interferon therapy, peg-IFN or ribavirin (RBV) in combination with rituximab (RTX) was found to be more effective than peg-IFN or RBV alone in the treatment of HCV-associated MC (78, 79). Although the discovery of new DAAs has revolutionized the therapeutic approach, data on their efficacy in patients with HCV-associated cryoglobulinemic vasculitis and GN are disappointing, probably due to the inability of the drugs to suppress the immune-mediated process (80). RTX, in combination with DAA drugs, seems to have some impact on HCV-related cryoglobulinemic vasculitis. However, with the new generation of DAAs, the percentage of patients needing to receive concomitant immunosuppression is decreasing. Forty-three percent of

patients treated with first-generation protease inhibitors required RTX or steroids, compared to 17% of patients treated with sofosbuvir (79, 81). In more recent studies on sofosbuvir-based therapy, only 4.5% of patients required RTX (82, 83). In severe forms of cryovasculitis, it is necessary to use immunosuppression as a rescue therapy during treatment with DAAs (84), and complete remission of MC in response to combination therapy with DAA and RTX has been reported (85). All these findings have been incorporated in the recently published KDIGO guidelines (86). Accordingly, the recommendation is that patients with HCV-related glomerular disease should be initially treated with DAA. For those patients who have flares or rapidly progressive kidney failure, in addition to DAA, immunosuppression should be used with or without plasma exchange. In the case of lack of response to DAA therapy, RTX treatment is recommended.

HCV treatment in patients with CKD

HCV infection is associated with a higher incidence of decreased eGFR, increased risk of CKD progression, and mortality. In a meta-analysis that included 890,560 patients, seropositive patients against HCV had a 70% increased risk of reduced eGFR (87) and in the REVEAL study, HCV-positive patients had a lower eGFR and an increased risk of ESRD (47, 88). These data were confirmed by another study performed on US veterans (89). In this study, HCV positivity was associated with a deterioration of kidney function and the development of ESRD. Also, the NHANES III study confirmed a significantly higher microalbuminuria in HCV-positive patients (90). In addition to specific renal diseases, cardiovascular disease and diabetes mellitus account for the rapid evolution of CKD in HCV patients (31). The discovery of DAA agents represented a relevant step in the evolution of HCV treatment by allowing to treat CKD patients independently of the existence of an HCV-related specific nephropathy. The aim of HCV treatment is to reach a stable SVR over time as documented by HCV serology and nucleic acid testing (NAT), 3 months after the end of treatment (91).

Most of the DAA studies in the general population included patients with normal renal function and randomized controlled trials (RCTs) for CKD included patients with stages 4 and 5. As patients with CKD stages 1–3 are not considered a priority (87), data for these patients derive from post-marketing or real-world studies (92). In the TRIO Network, the combination of elbasvir and grazoprevir (EBR/GZR) obtained a stable SVR, and about 50% were CKD stages 1–3 patients (93). The same combination was equally effective in a different study (94). The HCV TARGET database (73) did not find any difference in SVR rates comparing different CKD stages. This study as well as a study by Sise et al. (95) analyzed a sofosbuvir-based regimen. In this study, a sofosbuvir-based regimen reached a stable SVR independently of the CKD stage. To date, the use of sofosbuvir is

only recommended for patients with an eGFR >30/mL/min, and investigations on the use of sofosbuvir in patients with ESRD are underway. Based on pharmacokinetic studies, sofosbuvir may accumulate in ESRD patients reaching an area under the curve (AUC) increase of 171%. Reports on safety of sofosbuvir in patients with ESRD are still sparse, and the available data are based on few studies with limited number of patients (96–98).

The use of DAAs in patients with CKD stages 4 and 5 (< 30/mL/min) is confirmed by several studies and RCTs. In the C-SURFER study (99), a combination of grazoprevir and elbasvir achieved a stable SVR in ESRD patients affected by HCV genotype 1. This combination therapy was approved by the FDA in 2016. A retrospective analysis of this combination therapy confirmed its safety and efficacy (100). This is currently the recommended treatment for ESRD patients affected by genotype 1 or 4 (Table 4) (6). In August 2017, the FDA approved the pan-genotypic combination of glecaprevir (NS3/4 protease inhibitor) and pibrentasvir (NS5A inhibitor). The EXPEDITION-4 RCT investigated this combination (101). The combination therapy administered to ESRD patients affected by genotypes 1–6 resulted in a stable SVR in 98% of patients, with few adverse events. The results of EXPEDITION-4 are encouraging but need confirmatory

studies because of the small numbers of patients affected by genotypes 5 and 6. Even though DAA therapy is expensive, recent studies documented that grazoprevir/elbasvir is cost-effective in the United States (102) and France (103).

The recently published KDIGO guidelines (104) are in line with these studies and recommend a combination of grazoprevir/elbasvir for HCV patients with CKD stages 4 and 5 (Table 5) (104). A relevant question is: “how and when a dialysis patient should be treated?” This is discussed by Davis et al. (105). RNA-positive patients with an active infection should undergo a complete evaluation of liver disease. If they are affected by a severe decompensate cirrhosis, they should be listed for a combined liver–kidney transplant; otherwise, they can remain on dialysis and get treated for HCV. If the liver evaluation shows only a mild activity with mild fibrosis, then the patients are transplant candidates, and there are two options. First, patients who are transplant candidates and have living donors should be treated immediately for HCV infection and transplanted if found negative. Second, patients who do not have living donors could be listed for HCV-positive cadaver donor if the transplant center accepts this activity or should wait for a cadaver donor and treat HCV while on dialysis and waiting (Figure 3). However, dialysis patients who are not transplant candidates should also

Table 4. Recommended direct-acting therapies by eGFR and viral genotype (AASLD/IDSA) (6)

Kidney function	Viral genotype	Recommended DAAs	Rating of recommendation
eGFR >30 mL/min per 1.73 m ²	1, 3	Daclatasvir (60 mg)	1, A
	1, 4	Daily fixed-dose combination of elbasvir (50 mg)/ grazoprevir (100 mg)	
	1–6	Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)	
	1, 4, 5, 6	Daily fixed-dose combination of ledipasvir (90 mg)/ sofosbuvir (400 mg)	
	1–6	Daily fixed-dose combination of sofosbuvir (400 mg)/ velpatasvir (100 mg)	
	1	Simeprevir (150 mg)	
	1–6	Daily fixed-dose combination of sofosbuvir (400 mg)/ velpatasvir (100 mg)/ voxilaprevir (100 mg)	
eGFR < 30 mL/min per 1.73 m ²	1, 4	Daily fixed-dose combination of elbasvir (50 mg)/ grazoprevir (100 mg)	1, B
	1–6	Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)	1, B
	1–4	Sofosbuvir (400 mg)	

AASLD/IDSA, American Association for the Study of Liver Disease/ Infectious Diseases Society of America; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate.

Table 5. Recommended direct-acting antiviral (DAA) treatment regimens for patients with chronic kidney disease G4-G5 and kidney transplant recipients by hepatitis C virus genotype (104)

Kidney function	HCV genotype	Recommended regimen	Strength of evidence	Alternate regimen	Strength of evidence
CKD G4–G5 (GFR <30 mL/min per 1.73 m ²) including kidney transplant	1a	Grazoprevir/elbasvir	1B	Ritonavir boosted paritaprevir, ombitasvir and dasabuvir	2D
		Glecaprevir/pibrentasvir	1B	Daclatasvir/asunaprevir	2C
	1b	Grazoprevir/elbasvir	1B	Ritonavir boosted paritaprevir, ombitasvir and dasabuvir	2D
		Glecaprevir/pibrentasvir	1B	Daclatasvir/asunaprevir	2C
	2, 3	Glecaprevir/pibrentasvir	1B		
	4	Grazoprevir/elbasvir	2D		
		Glecaprevir/pibrentasvir	1B		
	5, 6	Glecaprevir/pibrentasvir	2D		
KTR (GFR > 30 mL/min per 1.73 m ²)	1a	Sofosbuvir with ledipasvir, daclatasvir, or simeprevir	1B	Sofosbuvir/ribavirin	2D
		Glecaprevir/pibrentasvir	1C		
	1b	Sofosbuvir with ledipasvir, daclatasvir, or simeprevir	1B		
		Glecaprevir/pibrentasvir	1C		
	2, 3, 5, 6	Glecaprevir/pibrentasvir	1D	Sofosbuvir/daclatasvir/ribavirin	2D
	4	Sofosbuvir with ledipasvir, daclatasvir, or simeprevir	1D		
		Glecaprevir/pibrentasvir	1D		

KTR, Kiney transplant; CKD, chronic kidney disease; HCV, hepatitis C virus.

receive treatment for HCV infection. We have already highlighted that HCV dialysis patients are affected by multiple hepatic and extrahepatic adverse events. Early data suggest a benefit with the new DAAs. The treatment cost does not justify withdrawing treatment for these patients, even if they are not transplant candidates (106).

HCV treatment in transplant candidates before or after transplantation

The optimal timing to treat kidney transplant candidates is a matter of debate. On one hand, treatment before transplantation decreases early posttransplant complications related to HCV infection. On the other hand, postponing treatment opens the possibility of transplanting a kidney from an

HCV-positive donor, which means there is a shorter waiting time. Whether or not to treat HCV dialysis patients before transplantation is a concern that should be based on several considerations, such as the extent of liver damage, availability of living donors, and extrahepatic manifestations of HCV. Patients with early cirrhosis without portal hypertension are considered for kidney-alone transplantation and the decision to treat with DAAs prior to transplantation also relies on other factors such as the availability of a living donor (107). In this scenario, it is better to treat before transplant if the transplant itself is not imminent. Based on several studies, it could be said that the delay of transplantation should be individualized according to specific conditions (108, 109). Extrahepatic manifestations of HCV include mixed cryoglobulinemic syndrome (MCS) and lymphoproliferative disorders. Patients

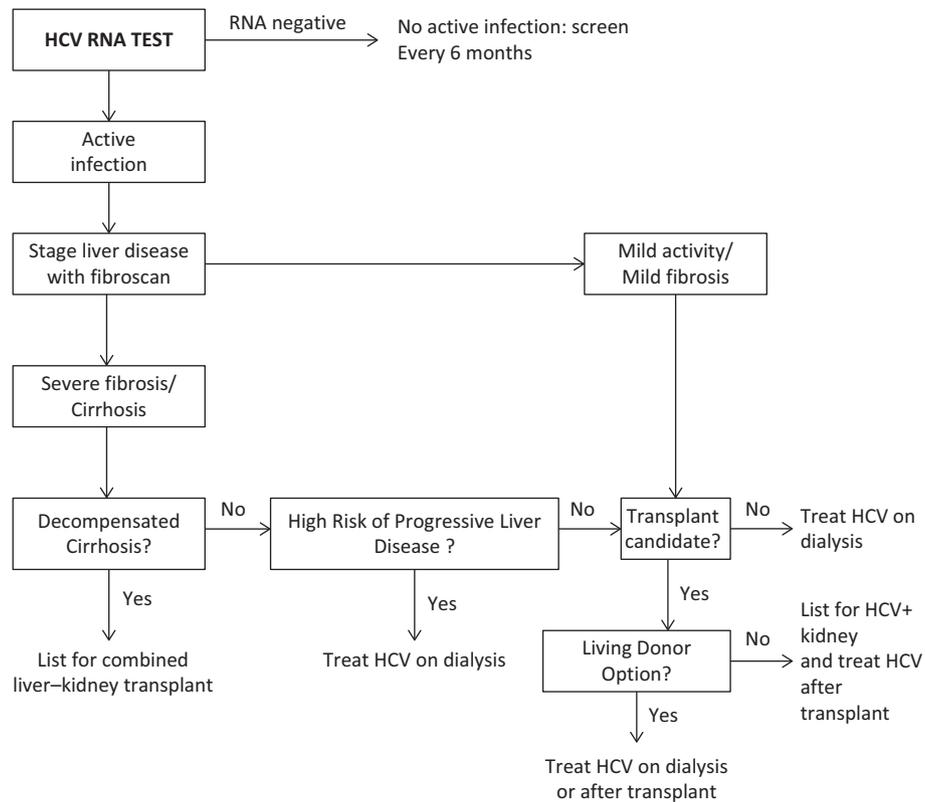


Figure 3. Algorithm for hepatitis C virus antibody positive dialysis patients to determine timing of treatment (105).

with active HCV-associated MCS should undergo treatment before transplantation in order to avoid further complications (107). A regression of lymphoproliferative disorders related to HCV has been documented in 75% of patients (110). These patients too should be treated before transplantation.

The advent of DAAs made it possible to transplant HCV-positive kidneys into HCV-positive recipients. Before the advent of DAAs, a large study documented the long-term survival of patients transplanted with HCV-positive kidney (111). In the era of DAA therapy, several studies have documented that transplantation of an HCV-positive kidney into an HCV-positive recipient, and treatment with DAA post-transplant, had excellent outcomes, with stable SVR rates (112, 113). In addition, DAAs have allowed the transplantation of HCV-infected kidneys into HCV-uninfected recipients. In addition to individual reports, two main studies examined this strategy. In the THINKER trial, patients were enrolled and treated a few days after transplantation with elbasvir and grazoprevir. Recipients became positive after transplantation, but an SVR was obtained in all the patients at 3 months (114). In the EXPANDER-1 trial, eight patients were transplanted in the same way. DAA therapy obtained an SVR in 3 months (115).

Colombo et al. (116) performed a phase 2 RCT to evaluate the safety and efficacy of the combination of ledipasvir

and sofosbuvir in 114 renal transplant patients with HCV genotype 1 or 4. SVR was obtained in all the patients with an excellent renal outcome. Saxena et al. (117) reported the efficacy of DAA therapy in 443 patients who received either kidney transplant or liver transplant, or combined liver-kidney transplant. The majority of patients were treated with sofosbuvir/ledipasvir with or without RBV. DAA therapy was effective and safe in both kidney and liver transplantation. Reau et al. (118) in the MAGELLAN 2 study investigated the safety and efficacy of glecaprevir and pibrentasvir in liver or kidney transplant patients. SVR was achieved in 99% of patients, with a 100% kidney and graft survival. The 2017 AASLD (119) published the guidelines for kidney transplant patients, and the KDIGO guidelines recall what has been described above on the management of HCV-infected patients before and after kidney transplantation (Table 5) (120). One important concern with the new DAAs in kidney transplant patients is the drug interactions with the immunosuppressive agents. Cyclosporine, tacrolimus, and sirolimus are metabolized in the liver by the cytochrome 450. As a result, for most DAAs, a substrate competition may occur, influencing their elimination. A careful dosage of DAAs and immunosuppressive agents is therefore recommended (120).

Conclusion

HCV infection is characterized by several extrahepatic disorders, among which renal disorders are frequent and relevant. Some of the HCV-related renal disorders include cryoglobulinemic GN, especially MPGN, higher incidence of progression to ESRD, and CKD-related mortality rate. The introduction of DAAs has revolutionized the management of HCV-mediated renal disorders. Cryoglobulinemic GN may be controlled using immunosuppressants in addition to DAAs. Patients at various stages of CKD may be treated for HCV to slow down the progression towards ESRD. Renal transplantation may be performed in HCV patients by treating them with DAAs before or soon after transplantation. Finally, HCV-positive kidneys may be given to HCV-positive or HCV-negative recipients by following specific guidelines.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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