

Hepatitis C Therapy in Renal Patients: Who, How, When?

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ABSTRACT

Renal patients are overexposed to hepatitis C virus (HCV) infection. Hepatitis C virus infection may induce renal disease, i.e., cryoglobulinemic membrano-proliferative glomerulopathy and non-cryoglobulinemic nephropathy. Hepatitis C virus impacts general outcomes in chronic kidney disease, dialysis or transplanted patients.

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Hepatitis C virus infection is now about to be only part of their medical history thanks to new direct acting antiviral drugs exhibiting as much as over 95% of sustained virological response. All HCV-infected patients potentially can receive the treatment. Control of the virus is associated with better outcomes in all cases, whatever the severity of the hepatic or renal disease. This article focuses on HCV-induced renal diseases, the reciprocal impact of HCV infection on the renal outcome and renal status in liver disease, use of new direct-acting antiviral drugs with dosage adaptations and the most recent safety data.

Keywords: Chronic kidney disease; Cryoglobulinemia; Dialysis; Direct acting antiviral agents; Hepatitis C; Membranoproliferative glomerulonephritis; Sustained virological response; Transplantation

INTRODUCTION

Hepatitis C virus (HCV) was discovered 25 years ago [1] and is now about to get a cure. In the meantime, the C virus has induced tremendous

morbidity and mortality mainly due to liver complications (cirrhosis, hepatocellular carcinoma). However, many extrahepatic manifestations [2] have been reported for chronic HCV infection with increased related morbidity and mortality, including cardiovascular diseases, type 2 diabetes and insulin resistance, neurocognitive dysfunction, systemic vasculitis, B cell non-Hodgkin lymphoma and chronic kidney disease [3]. Today, some new challenges remain, particularly with regard to specific populations suffering from HCV infection, such as renal patients. Our article focuses on the specificities of screening, monitoring, assessing, treating and following up, in the context of HCV infection, persons living with chronic kidney disease, end-stage renal failure or a kidney graft.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

EPIDEMIOLOGY OF HEPATITIS C VIRUS INFECTION IN RENAL PATIENTS

Approximately 170 million people are infected with HCV worldwide and 2.35% of the total world population [4]. In dialysis patients, the prevalence of HCV infection has evolved dramatically over the last 10 years. In 2004, the Dialysis Outcomes and Practice Patterns Study (DOPPS) published the largest study analyzing the HCV serological status in 8615 randomly selected hemodialysis patients treated in 308 dialysis facilities (in 8 countries in Europe, HCV USA and Japan) [5]. It showed the HCV antibody prevalence to be 14.7% when unadjusted and 10.4% when adjusted for age, gender, race, time with end-stage renal disease, and alcohol or drug

abuse in the past 12 months. The updated DOPPS study [6] found a very low prevalence of HCV treatment in dialysis patients as only 1% of the 4589 patients with available prescription data were receiving HCV medications. Among a subset of 617 HCV patients known to be on the waiting list for renal transplantation, only 3.7% were receiving HCV treatment. In the DOPPS study, the seropositivity for HCV was associated with black race [odds ratio (OR) = 1.93, $P < 0.0001$], male gender (OR = 1.18, $P = 0.01$), diabetes mellitus (OR = 1.18, $P = 0.03$), a history of gastrointestinal bleeding (OR = 1.22, $P = 0.06$), HBV infection (OR = 2.56, $P < 0.0001$) and prior renal transplant (OR = 1.34, $P = 0.01$). Drug and alcohol abuse, as reported during the 12 months prior to data collection, was also associated with HCV seropositivity (OR = 2.44, $P < 0.0001$ and 1.75, $P = 0.0001$, respectively). At that time, the risk of seroconversion was variable despite infection control measures, and HCV outcomes varied by patient characteristics, country and hemodialysis facility practice patterns. No consensus was available with regard to the need for hemodialysis patient isolation and dedicated dialysis machines to prevent HCV transmission, in addition to blood-borne precautions [5]. Adjusted HCV seroconversions/100 patient-years ranged from 1.2 (0.7–2.0) in the UK to 3.9 (2.9–5.2) in Italy. In 55.6% of facilities, the mean seroconversion rate was 0 per 100 patient-years. Seroconversion was mostly associated with the prevalence of HCV in the facility and with black race [relative risk (RR) = 1.42, $P = 0.05$], duration of end-stage renal disease (ESRD) therapy by year [with a 4% higher risk of seroconversion ($P = 0.007$)] and HIV/AIDS or HBV co-infection (RR = 3.29, $P = 0.006$ and RR = 2.16, $P = 0.001$, respectively). The authors concluded that this study provided evidence for nosocomial

transmission of HCV in dialysis facilities but did not demonstrate that isolation of patients infected with HCV was associated with a decreased risk of HCV seroconversion. The major drawback in this work was the absence of HCV RNA analysis.

A more recent analysis, the DOPPS 5 study (2012–2015) [6], included around 500 facilities and 17,000 patients in 21 countries. It showed that HCV prevalence among hemodialysis patients has declined in recent years in many DOPPS countries but remains higher than in the general population with a prevalence of 9.5% (in 11,394 patients). We generated the most recent analysis of the prevalence and incidence of HCV and HBV infections in end-stage renal disease patients in France from the REIN registry, a national prospective cohort including 72,948 patients who started dialysis or were preemptively transplanted. We found significantly lower prevalence of both HBV [1.41% (95% CI 1.32–1.49)] and HCV infection [0.84% (95% CI 0.78–0.91)] [7].

Transplanted patients are also exposed to HCV infection, mostly through their treatment with dialysis. However, a decrease in the frequency of HCV infection during dialysis has been mirrored by a decreased rate of HCV infection acquisition following renal transplantation [8].

CLINICAL INVOLVEMENT OF KIDNEY DURING HEPATITIS C VIRUS INFECTION

Mixed Cryoglobulinemia Vasculitis

Mixed cryoglobulinemia vasculitis (CryoVas) [9]—a small vessel vasculitis involving mainly the skin, joints, peripheral nerve system and kidneys—is mainly due to HCV infection

(70–80% of cases). The CryoVas may express mild symptoms (purpura, arthralgia) or more severe life-threatening complications (glomerulonephritis, widespread vasculitis). Renal involvement is an acute or chronic type-I membranoproliferative glomerulonephritis (GNMP) with subendothelial deposits (70–80% of cases), and it is strongly associated with type II IgM kappa mixed cryoglobulinemia [10]. Patients present with proteinuria, microscopic hematuria, a variable degree of renal insufficiency and new-onset arterial hypertension. Acute nephrotic or nephritic syndrome can also reveal CryoVas renal involvement. Early serum complement component levels (C1q, C4) are very low. Chronic renal insufficiency may develop in 10–20% of HCV-CryoVas patients. The pathological features are characterized by important monocyte infiltrates with double contours of the basement membrane and large, eosinophilic and amorphous intraluminal thrombi. Indirect immunofluorescence shows intraglomerular subendothelial deposits of IgG, IgM and complement components.

Cryoglobulinemia is confirmed by the detection of protein precipitates in the patient's serum maintained at 4 °C for at least 7 days, which dissolved when heated at 37 °C. Biological improvement can be assessed by the quantification of cryoglobulinemia and C4 and CH50 levels [9]. During HCV infection, predictive factors for CryoVas are advanced age, longer duration of infection, type II mixed cryoglobulinemia, higher cryoglobulin serum levels and clonal B cell expansions in both the blood and liver [11]. The overall 5-year survival after the diagnosis of HCV-CryoVas ranges from 90% to 50%, the latter being reported in case of renal involvement [11–14]. In a retrospective Italian study of 231

HCV-CryoVas patients [12], 79 of 97 deaths were linked to vasculitis (46%, of which one-third were due to renal involvement). Life-threatening CryoVas complications are observed in up to 10% of the patients with almost two-thirds resulting in death [13]. HCV-CryoVas may result in progressive (renal involvement) or acute (pulmonary hemorrhage, gastrointestinal ischemia, cardiac, CNS involvement) life-threatening organ damage. The mortality rate of these manifestations ranges between 20% and 80% [14, 15]. Age older than 60 years at diagnosis, the presence of a renal failure, intestinal ischemia, pulmonary hemorrhage, high cryocrit levels and type II mixed cryoglobulinemia are associated with severe prognosis [13].

In HCV-infected patients, many factors have been described to predispose patients to a CryoVas. Interaction between the virus and immune cells directly modulates B- and T-cell function resulting in expansion of B-cell production of IgM with RF activity [16]. The CD4⁺CD25⁺FoxP3⁺ regulatory T cell number is significantly reduced [17, 18], possibly leading to the expansion of peripheral auto-reactive B-cells. HLA-DR11 is associated with HCV-CryoVas, whereas HLA-DR7 appears to protect patients from the production of type II mixed cryoglobulinemia [19]. In a large multicenter study significant associations were identified on chromosome 6, a SNP located within an intronic region of NOTCH4 ($p = 6.2 \times 10^{-9}$), and another was found in between HLA-DRB1 and HLA-DQA1 ($p = 1.2 \times 10^{-7}$) [20]. A higher percentage of a particular allele of the promoter of the B-cell activating factor and different expression patterns on circulating lymphocytes of microRNAs known to be involved in lymphoproliferative and/or autoimmune disorders have been shown [21, 22]. Specific virological factors have never been identified.

Non-Cryoglobulinemic Renal Involvement in HCV-Infected Patients

Other glomerular diseases in both native [23] and transplanted kidneys [24] have been more rarely reported. In a large case-control study in US hospitalized male veterans [25], there was a greater proportion of MPGN among patients with HCV (0.36% vs. 0.05%, $p < 0.0001$), but not of membranous glomerulopathy. HCV-infected patients showed a 40% higher prevalence of renal insufficiency compared with non-HCV-infected people [26]. Other large surveys also suggested an impact of HCV infection on the prevalence and incidence of kidney disease in the general population [26–30]. The HCV seropositive status was associated with low GFR (OR up to 2.80) and proteinuria (OR 1.14–1.99), independently of diabetes mellitus, arterial hypertension, obesity and dyslipidemia [31]. In a recent population-based cohort among 2,267,270 Taiwanese residents diagnosed with diabetes mellitus [32], the cumulative incidences of ESRD at 8 years in the HCV-treated, HCV-untreated and uninfected cohorts were 1.1%, 9.3% and 3.3%, respectively. As compared with the untreated cohort, HCV treatment was associated with an HR of 0.16 (0.07–0.33%) for ESRD. Recent information has also accumulated on the association between HCV and glomerular disease in the liver [33, 34] or kidney/liver [35] transplanted population. The natural history of these HCV-associated nephropathies is characterized by remission and relapsing phases. Finally, HIV-HCV coinfection was also linked with a significant increase in the risk of HIV-related kidney disease [36, 37].

The Kidney Disease Improving Global Outcomes (KDIGO) group recommends that all patients with chronic kidney disease should be tested for HCV [38]. The KDIGO also

recommended that patients with acute flares of CryoVas and MPGN be treated with IFN-based HCV treatment. No doubt with recent advances in HCV treatment and direct-acting agents (DAAs) on the market such recommendations should be updated, i.e., should recommend IFN-free HCV treatment for patients with CryoVas and MPGN. In HCV-CryoVas patients with kidney involvement, the addition of rituximab to antivirals showed greater renal response rates than antivirals alone [39, 40]. However, considering the great and very rapid virological efficacy of DAAs, the remaining place of rituximab in HCV-MPGN needs to be further studied.

Impact of CKD on Hepatitis C Outcomes

Several studies have demonstrated that dialysis is associated with an increased risk of all-cause and liver-related mortality [41–43]. In this population, cardiovascular disease remains the first cause for death. CKD always impacts the treatment of chronic diseases negatively because of the poorer drug tolerance, higher prevalence of side effects and complexity of drug dosage adaptation. Hepatitis C treatment has long been offered through peginterferon alpha associated with ribavirin with very poor tolerance and a high prevalence of anemia and depressive syndrome leading to anticipated resuming of therapy [42]. Of note, HCV-Cryovas patients who present a GNMP showed a lower response rate to IFN-based treatment, whereas they showed a higher benefit of rituximab.

In transplanted patients, immunosuppression has been associated with an increase of serum HCV-RNA levels [43], and contradictory results emerged from the histological data on hepatic fibrosis after kidney transplantation. Some observations

reported dramatically bad outcomes after kidney transplantation with fibrosing cholestatic hepatitis [44]. Survival after transplantation was reported to be impacted negatively by a predisposition to progressive liver disease [8]. Besides, onset of new diabetes is significantly increased after transplantation potentially leading to metabolic complications.

TREATMENT OF HEPATITIS C INFECTION

In Patients with HCV-CryoVas

The CryoVas manifestations respond dramatically to HCV cure after antiviral therapy with pegylated interferon (IFN) plus ribavirin [45–48]. In case of persistent mixed cryoglobulinemia after HCV cure, when relapse of vasculitis also occurs, a different condition should be considered, especially B-cell lymphoma [49]. A recent open-label French prospective study [50] showed the good efficacy of a combination therapy with Peg-IFN/ribavirin plus a NS3/4A protease inhibitor (boceprevir or telaprevir) in patients with HCV-CryoVas. At week 24 post-treatment, two-thirds of patients were complete clinical responders, and their HCV was cured. However, serious adverse events occurred in half of the patients. In a prospective Italian study [51], HCV-CryoVas patients treated with Peg-IFN/ribavirin/boceprevir for 48 weeks showed a dramatic reduction in the cryocrit values and improvement of CryoVas symptoms. Other DAAs such as the NS5B inhibitor sofosbuvir, NS3/4A inhibitor simeprevir and NS5A inhibitor daclatasvir have been more recently licensed. These agents facilitate the use of shortened courses of combination IFN-free therapy, showing SVR rates >95% and few toxicities. International guidelines [52] recommend that

treatment should be scheduled, not deferred, for patients with clinically significant extra-hepatic manifestations, like CryoVas. A very recent open-label cohort study enrolled 24 patients with HCV-CryoVas who received an all-oral IFN-free regimen with sofosbuvir (400 mg/day) and ribavirin (200–1400 mg/day) for 24 weeks [53]. At week 12 post-treatment, 85% of patients were in complete remission for the CryoVas and 74% had an SVR, with a low rate of serious adverse events. The cryoglobulin level decreased from 0.35 to 0.15 g/l, while the C4 serum level increased from 0.10 to 0.17 g/l. Among patients with kidney involvement, renal function improved in four out of five, proteinuria decreased from 1.09 (0.6–2.4) to 0.17 (0.07–0.25) g/day and hematuria disappeared in all cases. Another study reported 12 HCV-Cryovas patients treated with sofosbuvir-based regimens [54]. Median baseline serum creatinine was 0.97 mg/dl (range 0.7–2.47 mg/dl). Four patients received rituximab concurrently with DAA therapy. The SVR at 12 weeks post-treatment was 83%. Patients with glomerulonephritis who achieved SVR12 experienced an improvement in serum creatinine and reduction in proteinuria. Serious adverse events were infrequent (17%). The historical cohort in this study treated with pegylated-IFN and ribavirin experienced a 10% SVR12 rate and 50% experienced premature discontinuation due to adverse events.

Rituximab targets B-cells, which are responsible for cryoglobulin production and finally vasculitic lesions [55–59]. In a randomized controlled trial of HCV-CryoVas patients, rituximab showed better efficacy than immunosuppressive treatments or plasmapheresis [60]. Similar results have been reported in a placebo-controlled trial [61]. The use of rituximab was shown to be safe in HCV

patients, in contrast with what was observed in HBV-infected patients [62, 63]. Two controlled clinical trials showed that rituximab plus Peg-IFN/ribavirin compared to Peg-IFN/ribavirin led to a shorter time to clinical remission, better renal response rate and higher rates of cryoglobulin clearance [39, 40]. However, there are no data indicating the exact place of rituximab with the use of DAAs, particularly if an IFN-free DAA combination is used before or at the same time as rituximab therapy.

Low-dose corticosteroids may help to control arthralgia but do not succeed in case of major organ involvement. Other immunosuppressants should be given in case of refractory HCV-CryoVas associated with underlying B-cell lymphoma [64].

In CKD Patients and ESRD Patients (Including Dialysis and Transplantation): Use and Monitoring of DAAs

In the past decade, peginterferon and ribavirin were considered the mainstay of hepatitis C virus treatment in CKD patients despite a high prevalence of side effects and poor clinical and biological tolerance. New DAAs offer dramatically improved efficacy in the general population.

Hepatitis C treatment may be discussed at any time of the follow-up when the glomerular filtration rate decreases during dialysis treatment, before and after renal transplantation [65].

It is a matter of debate whether hepC therapy should occur before or after transplantation [65]. Drug-drug interactions will definitively make monitoring more complex after transplantation since the impact of DAAs on tubular transports and cytochrome metabolisms will dramatically impact the pharmacokinetic

properties of immunosuppressive drugs [66]. New strategies will now emerge with regard to HCV treatment before or after renal transplantation depending also on the availability of a living donor or not. In case of a living donor, it has been proposed that DDA's treatment should occur before transplantation in order to obtain SVR12. When there is no living donor available, some centers (with a signed consent from the patient) will offer an HCV-positive graft to the patient and begin DAA treatment after transplantation, therefore reducing waiting times significantly [65]. DAA's availability will definitely further change the organ allocation criteria.

The information on the efficacy and safety of DAAs for HCV therapy in patients with renal failure is limited, but DAAs have begun to show their indications in stage 4 and 5 CKD patients. One of the available combinations of DAAs approved for patients with $15 < \text{GFR} < 30 \text{ ml/min}$ is the paritaprevir/ritonavir plus ombitasvir combination [67]. In this study, HCV genotype 1 treatment-naïve patients (without cirrhosis) were included in an open-label treatment study if they had stage 4 or 5 CKD. Twenty patients received DAAs for 12 weeks in two groups ($N = 7$ for genotype 1a receiving the paritaprevir/ritonavir plus ombitasvir combination and $N = 13$ for genotype 1b receiving the paritaprevir/ritonavir plus ombitasvir plus ribavirin combination). Two patients failed to achieve SVR12, and the overall tolerance of the treatment was satisfying. The choice of the appropriated drug must take into account the viral genotype as well as the tolerance in patients with decreased GFR. It is noteworthy, for example, that the paritaprevir/ritonavir/ombitasvir/dasabuvir combination is approved for CKD only in genotype 1 patients and that the paritaprevir/

ritonavir/ombitasvir combination is only effective for HCV-4.

The other combination showing good efficacy and tolerability in CKD settings is described in the C-SURFER study [68]. In this multicenter phase III all oral combination of grazoprevir 100 mg/day (HCV NS3/4A inhibitor) and elbasvir 50 mg/day (HCV NS5A inhibitor), 99.1% SVR12 was obtained in HCV genotype 1 patients with stage 4 and 5 CKD and compensated cirrhosis. Treatment was generally well tolerated. Less than 1% of grazoprevir and elbasvir was renally excreted [69]. Patients treated with hemodialysis were included in this study, whereas no data have been published on peritoneal dialysis patients. The grazoprevir/elbasvir combination, with or without ribavirin, was recently approved by the FDA for the treatment of chronic HCV genotype 1 and 4 infections in adult patients and was granted breakthrough therapy designation for the treatment of chronic HCV genotype 1 infection in patients with end-stage renal disease on hemodialysis and for the treatment of chronic HCV genotype 4 infection [69, 70].

Other DAA combinations may be used in CKD patients with well-preserved renal function, such as sofosbuvir (NS5B polymerase inhibitor) together with simeprevir (NS3/4A protease inhibitor), daclatasvir or ledipasvir (both NS5A inhibitors) with expected efficacy comparable to that of the general population. However, decreased renal function was observed with sofosbuvir in patients with GFR below $45 \text{ ml/min}/1.73 \text{ m}^2$ [70]. An active metabolite of sofosbuvir is actively renally secreted, and therefore overexposure may be observed in CKD patients. Sofosbuvir is used at a 400-mg daily dosage in patients with GFR above $30 \text{ ml/min}/1.73 \text{ m}^2$. However, the

Table 1 Recent data on HCV direct-acting agent use in renal patients [74]

Drug class	Metabolism and elimination	Regular daily dosage	Dosage in CKD or dialysis	Published data ^a
Sofosbuvir [75] <i>N5S8 inhibitor</i>	Prodrug: extensive intracellular metabolism (pharmacologically active metabolites GS-461203 via phosphorylation) Dephosphorylated into inactive metabolite GS-331007 Elimination: kidney (78% GS-331007 and 3.5% sofosbuvir); feces (15%)	400 mg once daily	No drug dosage adaptation if GFR >30 ml/min/1.73 m ²	After one single dose of 400 mg, an increase AUC (171% and 451%, respectively for SOF and GS-331007) was observed in non-HCV-patients with severe renal impairment [75] In HCV non-cirrhotic, treatment-naïve patients with eGFR <30 ml/min/1.73 m ² , a fourfold exposure to GS-331007 with 200 mg SOF daily was observed. Two patients discontinued because of AE (grade 2 fatigue and grade 3 renal failure and pneumonia). One initiated dialysis while under treatment. Overall, 2 grade 3 and 1 grade 4 increase in creatinine under treatment. SOF exposure was 136% and GS-331007 603% compared to HCV patients without renal failure [76]
Simeprevir <i>N53/4A protease inhibitor</i>	Metabolism: hepatic; saturable, first pass Elimination: biliary excretion (91%); renal (<1%)	150 mg oral daily with food	No drug dosage adaptation if GFR >30 ml/min/1.73 m ²	1890 HCV patients in real-life conditions (longitudinal target study) received SOF regimens (10% of which exhibited CKD and 3% needed dialysis), 42% cirrhotic. Serious adverse events were highest in patients with GFR 31–45 ml/min/1.73 m ² (23%). Compared to patients with mild renal impairment, those with severe impairment more frequently experienced anemia, acute renal failure and serious adverse effects even in ribavirin-free regimen patients [77] SOF 400 mg plus SIM 150 mg daily for 12 weeks in 17 dialysis or stage 4 CKD patients with hepatitis C (47% cirrhotic); treatment was overall well tolerated with no treatment discontinuations reported. Four (24%) patients reported mild AE [73]
Ledipasvir <i>N5SA inhibitor (co-formulation with Sofosbuvir)</i>	Metabolism: hepatic, minimal, not CYP450 mediated Elimination: feces (70%); urine (<1%)	90 mg oral daily	No drug dosage adaptation if GFR >30 ml/min/1.73 m ²	In HCV-negative patients with severe renal impairment (GFR <29 ml/min/1.73 m ²) receiving SIM, <i>C_{max}</i> and <i>AUC_{0–24 h}</i> were 34 and 62% higher compared to patients with normal renal function [78] In HCV-negative patients with severe renal impairment (GFR <30 ml/min/1.73 m ²) receiving LED (single dose) no differences in pharmacokinetics parameters were found [79]

Table 1 continued

Drug class	Metabolism and elimination	Regular daily dosage	Dosage in CKD or dialysis	Published data ^a
Dactasvir <i>N5SA replication complex inhibitor</i>	Metabolism: hepatic Elimination: feces (88%); urine (7%)	60 mg oral daily	No drug dosage adaptation if GFR >30 ml/min/1.73 m ²	A single dosage in HCV-negative individuals with CKD or ESRD showed a 60 and 80% higher AUC of DCV, respectively In patients in dialysis; no serious adverse events were observed despite a 27% increase in AUC compared to matched healthy controls [80]
Paritaprevir/ritonavir/ombitasvir/dasabuvir <i>NS3/4A HCV protease inhibitor</i>	Metabolism: hepatic Elimination: feces (>86%); renal (11.3%)	Two tablets of 75 mg/50 mg/12.5 mg oral daily + 250 mg twice daily	No drug dosage adaptation if GFR >30 ml/min/1.73 m ²	A single-dose pharmacokinetic study showed no clinically significant changes in any of the four drugs in severe renal impairment patients despite increase in <i>AUC24hour</i> [81, 82]
<i>HIV protease inhibitor</i> <i>N5SA inhibitor + non-nucleoside HCV polymerase inhibitor</i>				Ruby-1 trial: 20 patients naïve, HCV, non-cirrhotic, with advanced CKD (stage 4, <i>n</i> = 7) or dialysis (<i>n</i> = 13); most adverse events were mild to moderate; no study discontinuation, no treatment-related serious adverse event [83]
Grazoprevir <i>2nd generation HCV NS3/4A protease inhibitor</i>	Elimination: <1% of both drugs renally eliminated	GZR 100 mg and EBR 50 mg co-formulation daily	No drug dosage adaptation in case of renal failure	Healthy volunteers with severe renal impairment and dialysis; the treatment showed 65% and 86% increase in <i>AUC</i> , respectively for GZR and EBR. Dialysis patients showed same GZR/EBR exposure as matched subjects with normal renal function [84]
Elbasvir <i>N5SA inhibitor</i>				Placebo-controlled trial (C-Surfer study) 224 patients were randomized to immediate or deferred treatment with GZR/EBR. All patients on inclusion had a GFR <30 ml/min or in dialysis. The overall safety of the HCV therapy was very good with no discontinuation of study drug due to adverse events. AEs such as headache, nausea, diarrhea, etc., were equally distributed between patients receiving study drug versus placebo [85]

HCV hepatitis C virus, CKD chronic kidney disease, ESRD end-stage renal disease, AE adverse event, GFR glomerular filtration rate, SOF sofosbuvir, LED ledipasvir, SIM simeprevir, DCV daclatasvir, GZR grazoprevir, EBR elbasvir
^a Most studies were designed to evaluate efficacy as a primary endpoint—low number of patients

Table 2 Recent published guidelines for use of DAAs in CKD patients with comments from the latest publications**AASLD 2015**

For patients with mild to moderate renal impairment (GFR >30–80 ml/min), no dosage adjustment is required when using sofosbuvir, simeprevir, a fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) to treat or retreat HCV infection in patients with appropriate genotypes (I-A)

For treatment-naïve patients with HCV genotype 1 without cirrhosis with GFR <30 ml/min, treatment with the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with (1a) or without (1b) RBV (200 mg) once daily is recommended

RBV should only be given if the baseline hemoglobin level is greater than 10 g/dl

For patients with moderate renal impairment (eGFR 30–50 ml/min), initial RBV dosing should be 200 or 400 mg alternating every other day

For patients with severe renal impairment or who are on hemodialysis (eGFR <30 ml/min), initial RBV dosing should be 200 mg daily (II-B)

EASL 2015 Hepatitis C guidelines in hemodialysis patients

Simeprevir, daclatasvir and the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir are cleared by hepatic metabolism and can be used in patients with severe renal disease (A1)

Sofosbuvir should not be administered to patients with an eGFR <30 ml/min/1.73 m² or with end-stage renal disease until more data are available (B2)

The need for dose adjustments for the approved HCV DAAs in patients on dialysis is unknown. No safety dosing and efficacy data are available in this population

These drugs should thus be used with extreme caution in patients with severe renal disease and only in extreme life-threatening situations for patients on dialysis (B1)

Hemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy (B1)

Hemodialysis patients should receive an IFN-free, if possible ribavirin-free regimen for 12 weeks in patients without cirrhosis, for 24 weeks in patients with cirrhosis (B1)

authors tested a full dose or half dose of sofosbuvir in stage 4 or 5 patients (on dialysis or not) despite the exclusive renal elimination pathway [71, 72]. They showed no discontinuation due to side effects and no significant adverse events in small groups of patients. These results need to be confirmed in larger populations of CKD patients.

Despite better efficacy and good tolerance in CKD patients, DAAs may not be available, and depending on the local conditions, older

therapies such as PEG-interferons could still be offered with much less chance of SVR but at a lesser cost.

Other oral DDA combinations may be used in renal patients based on their hepatic metabolism. The risk of renal pharmacokinetic modifications in cirrhotic patients is high, and DAAs with hepatic metabolism in this context may not guarantee renal safety.

The HCV lifecycle can be blocked at many steps. HCV DAAs on the market or in clinical

development include NS3-4A protease inhibitors, nucleotide analog inhibitors of HCV RNA-dependent RNA polymerase (RdRp), non-nucleoside inhibitors of HCV RdRp and inhibitors of the non-structural 5A (NS5A) protein. These drugs differ in their activity against the different HCV genotypes and their barrier to resistance. They also differ in terms of the hepatic and renal metabolism. Some good reviews offer tables that detail drug dosage adaptations in renal failure [73]. In Table 1, we give a recent update of DAA use in renal patients. However, many other studies are ongoing that will allow a better knowledge of their safety in real-life conditions. New guidelines have been released with regard to hepatitis C treatment from both European and American societies (Table 2).

Unsolved Questions

In the context of HCV-CryoVas, considering the very rapid and potent virological efficacy of the new DAA combination (i.e., SVR >95%, viremia negative in <4 weeks) and the well-demonstrated correlation between SVR and clinical response, the exact place of rituximab, plasmapheresis or other immunosuppressive drugs remains to be defined.

In the context of a chronic renal insufficiency in HCV-infected patients not related to HCV-CryoVas, the role and impact of new DAA combinations on kidney function should be analyzed in large prospective studies with mid- and long-term follow-up, including GFR, proteinuria and hematuria.

CONCLUSION

New DAAs make the future of patients living with hepatitis C very exciting with a promise

of a cure from the viral infection. Major challenges for the clinicians remain optimal use of the new drugs and further monitoring of chronic kidney disease patients living with sustained viral response to ensure long-term renal protection.

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