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Hepatitis C virus infection and chronic kidney disease: time for reappraisal

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Abbreviations: HCV (hepatitis C virus), SVR (sustained viral response), DAAs (direct acting antiviral agents)

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Abstract

Hepatitis C virus (HCV) infection is associated with tremendous morbidity and mortality due to liver complications. HCV infection is also associated with many extrahepatic manifestations including cardiovascular diseases, glucose metabolism impairment, cryoglobulinemia vasculitis, B cell non Hodgkin lymphoma and chronic kidney disease (CKD). Many studies have shown a strong association between HCV and CKD, by reporting (i) an increased prevalence of HCV infection in patients on hemodialysis, (ii) an increased incidence of CKD and proteinuria in HCV infected patients, and (iii) the development of membranoproliferative glomerulonephritis secondary to HCV-induced cryoglobulinemia vasculitis. The HCV seropositivity is found to be associated to an increased relative risk for all-cause and cardiovascular mortality in dialysis population. HCV seropositivity is linked to lower patient and graft survival after kidney transplantation. Such poor HCV-associated prognosis should have encourage clinicians to treat HCV in CKD patients. However, due to frequent side effects and poor efficacy of interferon-based treatments, very few HCV dialysis patients have received HCV medications until now. The emergence of new direct acting, interferon-free antiviral treatment, leading to HCV cure in most cases with a satisfactory safety profile, will shortly modify the management of HCV infection in CKD patients. In patients with a glomerular filtration rate (GFR) >30 mL/min, the choice of DAA is not restricted. In those with 30>GFR>15 mL/min, only Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir or Grazoprevir plus Elbasvir regimen are approved. In patients with end stage renal disease (GFR< 15 mL/min or dialysis), current data only allow to use Grazoprevir plus Elbasvir combination. No doubt these data will be modified in the future with the advent of new studies including larger cohorts of HCV patients with renal impairment.

Abstract: 272 words

Approximately 130-170 million people are infected with hepatitis C (HCV) worldwide, 2.35% of the total world population. HCV has induced tremendous morbidity and mortality mainly due to liver complications (cirrhosis, hepatocellular carcinoma). In addition, many extrahepatic manifestations have been reported to be associated to 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 [1,2]. Patients chronically infected by HCV do present a high risk of chronic renal impairment with increased morbidity and mortality linked to it. In addition, the presence of renal insufficiency, and even more if an end stage renal failure (ESRD) or a kidney transplant (KT), has long been a brake to use interferon (IFN) based treatment because of poor efficacy and tolerance. Today, new direct acting antiviral (DAA) treatments lead to HCV cure in most patients with a very good safety profile. However, new challenges remain, particularly with regard to specific populations such as those with chronic kidney disease (CKD), ESRD or KT. Our review will focus on specificities of screening and treatment of such HCV infected patients with renal disease.

HCV and kidney disease

ESRD patients on regular dialysis showed high prevalence of HCV infection

In dialysis patients, the prevalence of HCV infection has evolved dramatically over the last ten years. The Dialysis Outcomes and Practice Patterns Study (DOPPS) has conducted in 2004 a prospective, observational study of adult hemodialysis patients randomly selected from 308 representative dialysis facilities in Europe and the United States [3]**.** Mean HCV facility prevalence rate was 13.5% and varied among countries from 2.6% to 22.9%. Increased HCV prevalence was associated with longer time on dialysis, male gender, black race, diabetes, hepatitis B virus (HBV) infection, prior renal transplant, and alcohol or substance abuse. Seroconversion was associated with an increase HCV prevalence in facility (RR=1.36, P<0.0001), but not with the isolation of HCV-infected patients (RR=1.01, P=0.99) [3]. A more recent analysis of the DOPPS study, including 49,762 hemodialysis patients enrolled between 1996 and 2011, showed a HCV sero-positivity prevalence of 9.5% [4]. More recent data came from a French national prospective cohort including 72,948 patients who

started dialysis or were preemptively kidney transplanted, that found a lower prevalence of HCV infection [0.84% (95% CI: 0.78 – 0.91)] [5].

HCV infected patients showed increased risk of chronic kidney disease

Studies are heterogeneous and controversial. Many data have been accumulated regarding the risk of CKD development in HCV infected patients. On one hand, a recent meta-analysis results of nine longitudinal studies (1,947 034 patients) demonstrated a relationship between HCV seropositivity and an increased incidence of CKD (defined by the incidence of stages 3-5 CKD or ESRD). The summary estimate for adjusted hazard ratio was 1.43 (95%CI 1.23; 1.63, P = 0.0001) [6]. In another meta-analysis, including fourteen studies (336,227 patients), Park et al. reported that HCV positive individuals had a 23% greater risk of having and/or developing CKD compared to uninfected individuals [7]. Consistently, in a nationwide cohort study including 293,480 Taiwanese residents among which 37,152 were HCV infected, multivariate-adjusted regression revealed that HCV treatment with pegylated interferon plus ribavirin was associated with a lower risk of ESRD after a 8 years follow-up (HR 0.15; 95% CI 0.07 to 0.31; p<0.001) [8]. These data were further confirmed by another recent study from Taiwan [9]. In a meta-analysis including 107,356 patients Fabrizi et al. found that HCV positive serology was an independent risk factor for proteinuria [adjusted OR 1.508 (95%CI 1.19; 1.89), P =0.0001) [6]. Anti-HCV positivity was significantly associated with proteinuria, independently of common metabolic factors such as diabetes mellitus, arterial hypertension, obesity, and dyslipidemia [6,10].

On the other hand, eight studies with cross-sectional design (788,027 patients) did not find a significant relationship between positive HCV serologic status and increased prevalence of CKD (mainly defined by eGFR<60ml/min/1.73m^2), with an adjusted OR of 1.16 (95%CI 0.98; 1.33, P = NS) [6]. In a retrospective cohort consisting of 71,528 Veterans, after a 6 years follow-up, 2,589 individuals recently HCV seroconverted were less likely to develop advanced CKD after controlling for traditional risk factors (HR 0.86; 95%CI 0.79, 0.92). HCV status was not significantly associated with progressive CKD (HR 0.93; 95% CI 0.86, 1.00)[11].

Overall, HCV infected patients appear at high risk for renal disease and therefore should probably benefit from close renal monitoring.

HCV mixed cryoglobulinemia vasculitis and kidney involvement

Mixed cryoglobulinemia vasculitis (CryoVas) is an immune complex small vessel vasculitis involving mainly the skin, the joints, the peripheral nerve system and the kidneys

[1,2]. Main symptoms include purpura, arthralgia, peripheral neuropathy, glomerulonephritis, and less commonly digestive, cardiac or central nervous system vasculitis. CryoVas is related to HCV infection in 70-80% of cases, mostly associated with the type II IgM kappa mixed cryoglobulinemia.

Renal manifestations are reported in 20-35% [12–14] of HCV-CryoVas patients. A large case-control study, carried out among U.S. male veterans hospitalized between 1992 and 1999, identified 34,204 patients who were hospitalized with HCV infection (cases) and 136,816 randomly selected patients without HCV infection (controls). There is a greater proportion of MPGN among patients with versus those without HCV infection (0.36% vs. 0.05%, $p<0.0001$) [15]. Most often a type-I membranoproliferative glomerulonephritis (MPGN) with sub-endothelial deposits is observed in patients with CryoVas and renal involvement [16]. Clinical presentation includes isolated proteinuria (<3 g/24 h), usually with microscopic hematuria (30%), a nephrotic syndrome (20%) or an acute nephritic syndrome (15%). Some patients present with a chronic renal insufficiency (10%), or an acute renal failure (10%) [17]. On kidney biopsy specimen, main features are characterized by important monocyte infiltrates with double contours of the basement membrane, large, eosinophilic and amorphous intra-luminal thrombi [17]. Diffuse MPGN (80% of cases) are characterized by duplication of glomerular basement membrane, interposition by mesangial cells and macrophages, subendothelial and mesangial deposition of immune reactants, mesangial expansion and proliferation with intracapillary leukocyte accumulation, and endoluminal hyaline pseudothrombi (corresponding to cryoglobulin precipitates). More than 50% of glomeruli are involved, and extracapillary proliferation and necrosis of the glomerular tuft can be found. Focal MPGN (10% of cases) involve less than 50% of glomeruli with endoluminal thrombi less frequently found. Mesangial MPGN (10% of cases) are characterized by diffuse mesangial expansion and proliferation without exsudation and endocapillary proliferation. Immunofluorescence shows diffuse, pseudolinear peripheral capillary wall and mesangial staining for IgM, IgG, and C3 with a relatively stronger staining for IgM and kappa light chain. Renal involvement complicated with ESRD is one of the most common reported cause of death of HCV-CryoVas patients [18-20]. In a recent study, 205/279 (73%) patients with life-threatening HCV-CryoVas had a renal failure. After a median follow up of 13 months, among patients with glomerulonephritis, 19% had a chronic renal failure, 4.8% required haemodialysis and 21% died [20]. Adjusted multivariate regression analysis identified age

(HR 1.036) and use of antiviral therapy (HR, 0.296) as the baseline risk factors associated with survival.

There are multiple immunological factors predisposing HCV infected patients to develop a CryoVas. Chronic stimulation of B cells by HCV directly modulates B- and T-cell function and results in polyclonal activation and expansion of B-cell producing IgM with RF activity. The expansion of clonal $CD21^{-/low}IgM^{+}CD27^{+}$ marginal zone like B cells was previously described [21]. $CD4^{+}CD25^{+}FoxP3^{+}$regulatory T cells levels are significantly reduced [22], which may account for the expansion of peripheral auto-reactive B-cell that leads to vasculitis. In a genome-wide association study significant associations were identified on chromosome 6 [23]. It has been shown a higher percentage of a particular allele of the promoter of the B-cell activating factor - known to be related to higher translational activity of the gene [24] - and different expression patterns on circulating lymphocytes of microRNAs [25]. In contrast, specific virological factors have not yet been identified. Other factors are related to the infection by HCV of peripheral blood mononuclear cells, including peripheral dendritic cells, monocytes, and macrophages [26]. A persistent viral stimulation enhances expression of lymphomagenesis-related genes, particularly the activation-induced cystidine deaminase which is critical for somatic hypermutation and could lead to polyclonal and later monoclonal expansion of B cells [27]. Under this trigger effect, oligo- or monoclonal IgM, that shares rheumatoid activity, is produced by a permanent clone of B cells which favors the appearance of immune-complexes, formed by circulating HCV, anti-HCV polyclonal IgG, and the monoclonal IgM itself. Due to the clonally restricted IgM, these cryoprecipitable immune-complexes also escape the erythrocyte transport system and directly impact hepatic and splenic macrophages, which are unable to process them due to abnormalities in the biogenesis of lysosomal enzymes [28,29]. The same abnormality is likely to occur in monocytes which are found to be engulfed with cryoglobulins at the electron microscopy examination of affected glomeruli. A murine model of cryoglobulinemic MPGN shows that macrophage ablation confers protection from mesangial expansion and does not affect cryoglobulin removal [30]. Based on these pathogenic principles, it seems unlikely that in patients with HCV-CryoVasc and a MPGN antiviral agents alone can effectively interfere with the all the pathogenic pathways, supporting the use of immunosuppressive drugs to stop the immune-mediated injury.

Prognosis of HCV infected patients with renal disease

Impact of HCV chronic infection on extra-liver outcomes in ESDR patients and kidney transplant recipients

Anti-HCV-positive serologic status is significantly associated with lower survival rates in dialysis populations. A meta-analysis, including fourteen observational studies involving 145,608 patients on long-term dialysis, found HCV seropositivity to be associated to an adjusted relative risk (RR) for all-cause mortality of 1.35 [95%CI; 1.25-1.47]. The adjusted RR for cardiovascular mortality was 1.26 (95%CI, 1.10-1.45) [31]. Consistently, a nationwide study in Taiwan revealed that untreated ESRD patients with HCV infection had an adjusted RR of death of 1.14 (95% CI, 1.04-1.25) [32]. HCV infected patients had higher rates of diabetes and ischemic heart disease compared with the uninfected cohort. The adjusted risk of death was markedly reduced in HCV treated (interferon-based treatment) patients without cirrhosis or hepatocellular carcinoma compared to the HCV untreated controls [HR 0.17 (0.04-0.68)]. In a very recent analysis of the Kaiser Permanente cohort (16,145 HCV infected adults and 2,179 HCV infected adults with CKD), CKD was associated with increased rates of death (RR=1.6; 95%CI 1.43-1.81), arrhythmia (1.89; 95%CI 1.69-2.11), acute myocardial infarction (2.39; 1.88-3.04), acute coronary syndrome (2.08; 1.61-2.68) and transient ischemic attack (1.97; 1.60-2.43). Rates of cardiomyopathy (2.95; 2.22-3.91) and congestive heart failure (3.88; 3.27-4.60) also increased with the addition of CKD (all RR adjusted for other cardiovascular risk factors). [33]

HCV infection was associated with an increased risk of arterial disease in patients on regular dialysis or kidney transplant recipient. After kidney transplantation, coronary flow reserve was significantly reduced in non-diabetic HCV patients compared with non-HCV patients [34]. HCV viremia was an independent factor of aortic stiffness in patients on regular dialysis [35]. A meta-analysis showed that HCV seropositivity is significantly linked to lower patient and graft survival after kidney transplantation. The adjusted RR of all-cause mortality was 1.85 (95% CI, 1.49-2.31) and of all-cause graft loss 1.76 (95%CI, 1.46-2.11) [36,37]. Another meta-analysis including eighteen studies showed that HCV-infected renal transplant recipients have worse outcomes (mortality and graft loss) than HCV-negative recipients [38].

HCV infection has been identified as an independent risk factor for graft loss and mortality in kidney transplantation patients. In a very recent retrospective study performed by the National Kidney and Transplant Institute in Philippines, authors found that patient

survival was significantly lower in the HCV-positive than in the HCV-negative group, with a mean duration of patient survival of 141 versus 155 versus months, respectively (p=0.05). The mean duration of kidney graft survival was 130 versus 137 months, respectively (NS). Short- and long-term outcomes including biopsy-proven acute rejection, transplant glomerulopathy, chronic allograft nephropathy, renal function, and proteinuria were similar in both groups [39]. In the largest published metaanalysis, a total of 8,348 HCV-infected renal transplant recipients (before or after kidney transplantation) were identified from 123,228 living and deceased renal transplant reciepients, as reported in 18 studies [38]. The combined hazard ratio in HCV-infected recipients was 1.69 (1.33-1.97, $p < 0.0001$) and 1.56 (1.22-2.004, $p < 0.0001$) times greater than that of HCV-negative recipients for mortality and graft loss, respectively.

Impact of chronic kidney disease on liver outcomes in HCV-infected patients

Several studies have suggested that ESRD patients on regular haemodialysis have lower liver fibrosis and inflammatory activity than matched controls without CKD [40–42]. The risk of liver inflammation was reported to be four times lower in haemodialysis patients than in matched controls [43]. Many hypothesis have been proposed such as the passage or trapping of viral particles during the dialysis or the production of cytokines (interferon-alpha, hepatocyte growth factor) with antiviral activities during the haemodialysis sessions [44]. The kidney transplantation did not prove to accelerate HCV related liver injury. In a retrospective cohort of HCV infected patients, 77% of thirty one kidney recipients who underwent multiple liver biopsies showed stable or improved liver histology whereas 62% of thirteen ESRD non transplanted patients showed a worsening of the liver fibrosis score [45]. Similar results were found in fifty one KTR, in which liver fibrosis remained stable or improved in 60% of cases. The controversial data may be related to the heterogeneous strength of immunosuppressive regimens across the studies. A low initial fibrosis stage and a high diversification of the HVR-1 region of HCV genome between the time of kidney transplantation and the first liver biopsy were independent factors associated with liver fibrosis regression [46–48].

Treatment of HCV infection in patients with renal disease

In ESRD patients before kidney transplantation

Before the era of IFN-free DAA combinations, the efficacy and safety of peg-IFN plus ribavirin treatment in HCV infected patients on long-term dialysis has been evaluated (meta-analysis of eleven studies, 287 patients). The summary estimate for SVR and dropout rate were 0.60 (95%CI, 0.47; 0.71) and 0.18 (95%CI, 0.08; 0.35), respectively [49]. Several studies have shown a better efficacy of peg-IFN plus ribavirin than IFN monotherapy in patients on regular dialysis [50–52]. Data of small HCV cohorts on maintenance haemodialysis treated with peg-IFN/ribavirin plus a NS3 protease inhibitor (telaprevir or boceprevir) showed an interesting virological efficacy but was associated with high rate of side effects. [53–55].

Due to the high frequency of adverse events of IFN-based therapies in the population with kidney disease, the recent results of trials evaluating the safety and efficacy of IFN-free DAA regimen are particularly interesting. Main pharmacokinetic characteristics and virological results are summarized in **Tables 1 and 2,** respectively.

Sofosbuvir (SOF), a NS5B inhibitor, is mainly eliminated by the kidney. Compared to patients with normal renal function, SOF AUC0-∞ was 170% higher and the principal metabolite (GS-331007, SOF-007) AUC0-∞ was 450% higher in those with eGFR <30 mL/min/1.73m^2. The use of SOF in patients with GFR <30 ml/min is not recommended. Despite the growing amount of information regarding the use of SOF in patients with CKD, the data come from small series of case or uncontrolled studies. A recent observational, prospective study enrolled twelve HCV-infected patients (83% with cirrhosis, 50% treatment naive) requiring haemodialysis, treated with a SOF-based regimen. Seven patients received sofosbuvir once daily and five patients three times a week, with a standard dose of daclatasvir (n=8), ledipasvir (n=1), simeprevir (n=2) and ribavirin (n=1). All patients showed higher SOF-007 plasma concentrations than those previously reported in patients with normal renal function, with a median SOF-007 extraction ratio of 52%. No SOF-007 accumulation was observed between haemodialysis sessions in patients receiving SOF once daily. The SOF-007 half-life calculated at treatment cessation was slightly higher than that reported in subjects with normal renal function (38 vs 27 hours). No serious adverse event was observed during the treatment courses. Ten patients achieved SVR12, i.e. 7/7 patients receiving SOF once daily and 3/5 receiving SOF three times a week [56]. In a recent cohort of seventeen ESRD patients (88% on dialysis) with genotype-1 HCV infection treated with full dose of SOF and simeprevir (47% cirrhosis, 80% naïve treatment), all patients achieved SVR12, none discontinued treatment for serious adverse-events and there were no dose adjustments of SOF

and/or simeprevir. [57]. Another recent study has confirmed the efficacy and safety of half-dose sofosbuvir plus simeprevir in HCV patients with end stage renal disease (i.e. SVR12 in 10/11 patients receiving SOF 200mg once daily and ¾ receiving SOF 400mg 3 times a week) [58,59]. In other small retrospective cohorts of SOF-based treatment in patients with eGFR≤30 mL/min/1.73m^2 or dialysed, SVR12 ranged from 67 to 100% with a satisfactory safety profile. In the multicentre, longitudinal TARGET cohort, seventy three patients treated with SOF-containing regimen (400mg plus simeprevir and/or ribavirin) had baseline eGFR≤45 mL/min/1.73m^2 (including 18 patients with baseline eGFR≤30 mL/min/1.73m^2 and 5 on haemodialysis). The SVR12 was achieved in 83% (95% CI: 71%-91%) vs. 82% (95% CI: 80%-84%) in patients with baseline eGFR ≤ 45 versus > 45 mL/min/1.73m^2, respectively. However, patients with eGFR ≤ 45 mL/min/1.73m^2 more frequently experienced anemia, worsening of renal function and serious adverse events. Baseline eGFR≤45 mL/min/1.73m^2 was a significant predictor of worsening renal function [RR: 4.71, (95%CI: 1.85-12.0); p=0.001)[60]. Consistently, Wanchoo et al. have recently reported a case of Harvoni-associated biopsy-proven acute interstitial nephritis in a patient with CKD [61]. EASL 2015 guidelines do not recommend the administration of SOF to patients with an eGFR < 30 ml/min/1.73 m^2 or with ESRD [62] **(Table 1).** Ledipasvir, a NS5A inhibitor, is not eliminated in urines and no increased Ledipasvir AUC was observed in patients with severe CKD. However, as Ledipasvir is co-formulated with SOF, data are insufficient to recommend its use in patients with severe CKD, i.e. with an eGFR < 30 ml/min/1.73 m^2.

Daclatasvir, a NS5A replication complex inhibitor, is allowed in patients with severe renal impairment. A recent case-control study has shown the efficacy of Daclastavir plus Asunaprevir in twenty eight HCV genotype 1 patients on regular haemodialysis (SVR12 100%) with similar rate of adverse events compared to matched controls [63]. Simeprevir, a NS3/4A protease mainly eliminated by the liver, has been evaluated in association with sofosbuvir, and data are too scarce in patients with severe renal impairment.

The Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir regimen is allowed without dose adjustment in patients with mild, moderate or severe renal impairment. Renal elimination is comprised between 2 and 11% according to the molecules. In the Ruby-1 trial, twenty naïve, non-cirrhotic, HCV patients with advanced CKD [stage 4 (n=6) or dialysis (n=14)] received Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (plus ribavirin in 13 patients). The SVR12 was 90%. One patient died unrelated to the treatment and one relapsed. Anemia occurred in nine patients receiving ribavirin and required ribavirin interruption in all. There was no DAA

related serious adverse event. The mean trough plasma concentrations of Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir in patients with stage 4 and 5 CKD were generally comparable to the values in HCV genotype 1 infected patients without ESRD [64].

The Grazoprevir plus Elbasvir regimen is to date the unique combination approved in ESRD. It has been evaluated in a large cohort of HCV-infected patients with severe renal involvement. Renal elimination is less than 1%. A phase 3 randomised study (C-SURFER) included two hundred and thirty five HCV genotype 1 patients with stage 4-5 CKD [76% with haemodialysis]. Patients were randomly assigned to the immediate treatment group with Grazoprevir 100mg plus Elbasvir 50mg or the deferred treatment group. Of note, 80% were treatment-naïve and only 6% had cirrhosis. The SVR12 in the immediate treatment group was 99% (115/116). In the deferred treatment group, the SVR12 was 98% (97/99). There were no discontinuations due to an adverse event in the immediate treatment group versus five in the deferred treatment group (one each of abdominal pain, elevated ALT and AST, atrial fibrillation with myocardial infarction, increased lipase, and acute myocardial infarction). There were four deaths, none considered related to study drug. Common adverse events (mainly headache, nausea, and fatigue) occurred at similar frequencies in patients receiving active and placebo drugs [65].

After kidney transplantation

Before the IFN-free DAA era, antiviral treatment was initiated before kidney transplantation due to an increased risk of allograft dysfunction/rejection with IFN-based therapy. A few studies have been conducted to evaluate the efficacy and the safety of DAAs after kidney transplantation. In two small size retrospective cohorts including mainly HCV genotype 1 kidney transplanted (50% with advanced liver fibrosis), the SVR12 was 100% in both studies with a good safety profile [66,67]. In this population, careful monitoring of blood level of calcineurin inhibitors are recommended as decreased levels of calcineurin inhibitors have been observed requiring drug dose adjustment [66]. Of note, blood levels of calcineurin inhibitors remained decreased three months after DAAs discontinuation. In a phase 2, open-label study, post-transplant patients with or without cirrhosis were randomized to receive Ledipasvir plus Sofosbuvir for either 12 weeks (n = 57) or 24 weeks (n = 57). The median time from transplant was 10 years out in the 12-week cohort and 12 years out in the 24-week cohort. Overall, 100% of the 12-week cohort achieved SVR12 and 96% of those in the 24-week cohort [68].

The particular case of HCV cryoglobulinemia vasculitis with renal involvement

Most HCV-Cryovas manifestations respond, at least partially, to clearance of HCV during antiviral therapy. Patients who relapse for HCV infection after responding to antiviral therapy usually relapse for the Cryovas with the return of viremia. Despite the successes with combination antiviral treatment, until recently HCV-Cryovas remained a severe disease, with reported 1-year, 3-year, 5-year, and 10-year survival rates are 96%, 86%, 75%, and 63%, respectively.

The cornerstone of HCV-Cryovas therapy has long been IFN. During the first decade after HCV discovery (1990-2000), treatment of HCV-Cryovas with IFN alone did not demonstrate efficacy in patients with renal involvement [69]. IFN plus ribavirin demonstrated efficacy on renal manifestations, i.e. loss of proteinuria and hematuria in patients with SVR [70–72]. During the decade 2000-2010, Peg-IFN plus ribavirin combination as compared with IFN plus ribavirin showed higher rates of complete clinical and virological responses [73]. Of note, a GFR < 70 ml/min was negatively associated with a complete clinical response. However, the tolerance was poor as peripheral neuropathy or skin ulcers may worsen under IFN-based therapy, and use of ribavirin frequently needed use of erythropoietin. More recent advances were reported with use of DAA. The first antiviral combination including a DAA was based on a combination of Peg-IFN, ribavirin, and a protease inhibitor (i.e. Boceprevir or Telaprevir) in HCV genotype 1 patients. Such combination showed a complete clinical response in up to 56.5 % of HCV-Cryovas patients [74,75]. Patients showed a dramatic reduction of the cryocrit values and increase of C4 level with an improvement of Cryovas symptoms. However, grade 3 and 4 adverse events (mainly anemia, neutropenia and thrombocytopenia) were observed in up to 43.5% and antiviral therapy discontinuation was required in one third of patients [74]. During the last two years, all oral IFN-free, DAA regimens have been used in HCV-Cryovas patients. Such regimen permitted to remove IFN from the combination which had the potential to exacerbate autoimmune disease states, including CryoVas. The VASCUVALDIC study enrolled twenty four patients with HCV-Cryovas [median age 56.5 years, 54% males, 50% cirrhotic] who received SOF plus ribavirin for twenty four weeks [76]. Seven patients also received immunosuppressive therapy, i.e. rituximab, corticosteroids, and plasmapheresis. Eighty seven percent of patients were complete clinical responders at week12 post-treatment. Of note, the complete clinical response was very rapid as it was noted at on-treatment week12 in two third of patients.

Kidney involvement with MPGN improved in four out of five patients. Daily proteinuria decreased from 1.09 to 0.17 g, hematuria disappeared in 4/4 cases, whereas median GFR remained stable (77.3 at baseline and 66.7 ml/min/1.73 m² at week 24). Only two (8%) serious adverse events were observed. Sise et al have reported a retrospective case series of twelve HCV-CryoVas patients treated with SOF-based regimens [median age 61 years, 58% males, 50% cirrhotic]. Median baseline serum creatinine was 0.97 mg/dL (range 0.7-2.47 mg/dL) [77]. Seven patients had evidence of renal involvement including five MPGN. Five of them had active glomerulonephritis at the onset of DAA. Four patients received Rituximab concurrent with DAA therapy. All patients had undetectable HCV RNA by week 4. A SVR12 was achieved in 10/12 (83%) patients. Individual eGFR changes in patients with active glomerulonephritis showed a positive impact in two out of seven patients; there was a reduction in proteinuria in 3/3 cases. Cryoglobulin levels decreased in 89% of patients, with a median percent decreasing from 1.5% to 0.5%, and completely disappeared in 4/9 cases. Only two (17%) patients experienced serious adverse events. Very recently, in a nationwide Italian study, Kondili et al reported the disappearance or improvement of more than 50% of CryoVas symptoms in 31/37 (84%) patients after DAA, with no specific details on kidney parameters [78]. A Canadian group described eleven patients with symptomatic HCV-CryoVas who received IFN-free DAA combinations (56 years old, 61% females, 57% cirrhotics) [79]. A full or partial clinical response of CryoVas symptoms was obtained in 91% of patients and a complete or partial immunological response in 81%. A full or partial renal response was noted in 80% with a decrease of creatinemia from 104 to 95 micromol/l, of proteinuria from 3.0 to 0.65 g/l as well as a decrease of hematuria. A serious adverse event was reported in only 12%.

Conversely, Cornella et al reported on five patients with HCV-CryoVas who received 24 weeks of triple therapy with PegIFN/ribavirin plus DAA (boceprevir, telaprevir or sofosbuvir). They found a good impact on main CryoVas manifestations but did not observe a rapid clearance of serum cryoglobulins [80].

Despite the unquestionable evidence of a viral etiology and the role of effective antivirals, immunosuppression is still regarded as a major treatment in HCV-CryoVas patients with renal involvement. In case of severe CryoVas with renal involvement or in patients with failure or contraindication to antiviral treatment, Rituximab - a monoclonal anti-CD20 antibody - targets activated B-cells, which are responsible for cryoglobulin production and finally Cryovas lesions. iRtuximab has a better efficacy than conventional immunosuppressive treatments (i.e., glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis) or placebo [11, 66]. Addition of rituximab to peg-IFN/ribavirin led to a

shorter time to clinical remission, better renal response rate, and higher rates of cryoglobulin clearance [12,14]. Of note, some patients may experience a severe flare of CryoVas after rituximab infusion, notably patients with high cryoglobulin levels [82]. The cumulative probability of survival in patients with CryoVas MPGN was less than 60% at 5 years and most deaths in the pre-Rituximab era were due to liver failure and infections [83,84]. A recently reported cohort of patients treated with an intensive "4 plus 2 Rituximab infusion protocol" showed a 75% survival rate at 6 years, with a 60% probability of remaining symptom-free for 10 years without any therapy[85].

Corticosteroids, used alone or in addition to IFN, did not favourably affect the response of HCV-CryoVas manifestations in controlled studies [86]. Plasmapheresis offers the advantage of removing the pathogenic cryoglobulins from the circulation. It is particularly effective for rapidly progressive glomerulonephritis. Immunosuppressive therapy is usually needed with plasma exchange in order to avoid the rebound increase in cryoglobulin serum level seen after discontinuation of apheresis. When used in combination with HCV treatment, plasmapheresis did not modify the virologic response if IFN was given after each plasma exchange session [87]. There is no available data to date with DAA.

Care of HCV in patients with chronic kidney disease in daily practice

1. Screening

Altogether, many studies provide convincing data that suggest (i) a high prevalence of HCV infection in CKD patients, with a high risk of contamination in kidney facilities, (ii) a strong relationship between HCV infection and renal involvement, with an increased risk of CKD in HCV infected patients, and (iii) a negative impact of HCV chronic infection on main renal and extra-renal outcomes. Therefore, on one hand, regular screening of renal involvement is mandatory in HCV infected patients, including scheduled dosages of proteinuria, hematuria and creatininemia. Of note, creatininemia may be underestimated in patients with severe liver disease and eGFR evaluation is needed. The estimation of GFR based on measurement of cystatin C may be of interest in this context. On the other hand, HCV infection should be searched in all patients with impaired renal function because of a negative impact of HCV chronic infection on renal and extra-renal outcomes, and the good impact of efficient HCV treatment.-The cost-effectiveness of these strategies should be further studied.

2. Treatment of HCV infection in CKD patients

a. Who should we treat?

On one hand, following the 2015 EASL guidelines, all treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy (grade A1), which includes also CKD patients [62]. On the other hand, the last Kidney Disease Improving Global Outcomes (KDIGO) guidelines published in 2008 (long time before the era of DAA) recommended IFN-based therapy only for KT with HCV infection in whom the benefits of treatment clearly outweigh the risks i.e. cholestatic fibrosing hepatitis, severe vasculitis, rapid cirrhosis [49,88]. Treatment of HCV was also strongly recommended at that time in renal transplant candidates, dialysis-dependent or not, because IFN-based regimens were contraindicated after KT. Updated DOPPS study in hemodialysis patients enrolled between 1996 and 2011, found that only 1% of the 4,589 dialysis patients with available prescription data were receiving HCV medications [4]. Recent approval of new DAAs, including IFN-free, ribavirin-free combinations, with a great virological efficacy and a satisfactory safety profile in ESRD patients, should shortly modify the landscape. Time for reappraisal has come including new guidelines for HCV screening and treatment in CKD patients. HCV-associated poor prognosis in ESRD patients on regular dialysis or in KT provides important data suggesting to consider antiviral treatment in CKD patients without an advanced liver fibrosis or a vasculitis. Treatment with DAAs should be proposed to any patient with renal impairment in order to (i) reduce the progression of the liver disease, especially after transplantation; (ii) reduce the risk of renal-related morbidity and mortality; (iii) reduce the risks of diabetes, cardio- or cerebrovascular disease and (iv) improve well-being [89]. With new KDIGO guidelines update, we may speculate that the recommendation should be to treat all the « priority » patients and to wait after renal transplantation for the others, especially in USA where the use of derogatory HCV positive allografts is a major issue. The financial issue remains a serious “obstacle” and further studies are needed to confirm the good safety of new DAA in ESRD patients in real life conditions.

b. How to treat?

There is no doubt that recent approval of new IFN-free, ribavirin-free DAA combinations should rapidly lead to new KDIGO guidelines [89]. Based on EASL 2015 recommendations [62], the type of DAA combination should take into account many factors

including HCV genotype, the presence of a cirrhosis, a previous and the Child Pugh grade of decompensation, and the response to a previous antiviral treatment. Considering the level of kidney insufficiency, when 60 > GFR > 30 mL/min/1.73m^2, SOF-based treatment, as well as Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir combination or Grazoprevir plus Elbasvir regimen may be given. When patients have a 30 > GFR > 15 mL/min/1.73m^2, only Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir or Grazoprevir plus Elbasvir regimen are approved. According to the package insert, the use of SOF-based treatment in patients with GFR < 30 mL/min is not recommended. However, when no other treatment is available, SOF may be used with caution. A close clinical and biological monitoring is mandatory including ECG, serum lactate and creatininemia (worsening kidney function observed in the TARGET cohort). Finally, when patients have an ESRD (GFR < 15 mL/min/1.73m^2 or dialysis patients), only Grazoprevir plus Elbasvir combination may be prescribed. For patients with kidney transplant, data are too scarce to support strong recommendations, although the choice of DAA combination should take into account potential drug-drug interaction.

In the context of HCV-CryoVas with kidney involvement, IFN-free DAA combination might be considered as induction therapy for patients with mild disease severity i.e. mesangial glomerulonephritis without organ or life threatening complications. The duration of antiviral therapy is 12 to 24 weeks according to the DAA regimen and predictive factors of virological response (i.e. liver cirrhosis, genotype 3, non-response to previous antiviral drugs). In patients presenting with worsening of renal function, combination therapy with rituximab plus IFN-free DAA might be recommended, with DAAs starting at the same time as rituximab. In case with a rapidly progressive glomerulonephritis frequently associated to digestive, cardiac, pulmonary and/or central nervous system involvement, plasmapheresis can have immediate beneficial effects. It should be combined with immunosuppression not only to avoid post-apheresis rebound of cryoglobulinemia but also because of the added effects of the anti-B lymphocyte activity of the standard immunosuppressive drugs (cyclophosphamide, and, more recently, mycophenolate mofetil). However, Rituximab alone or in combination with methylprednisolone pulses has proved to be safer and comparably effective in open studies [85]. In such cases, an unsolved issue is the time when to start DAAs, i.e. during or after the critical phase.

c. When to treat?

Before the onset of DAA, experts recommended to treat HCV in patients with ESRD before kidney transplantation due to the risk of kidney transplant dysfunction or rejection with

IFN-based therapy. Preliminary results of small cohorts suggest the safety and efficacy of DAA in KT. On one hand, potential drug-drug interactions with immunosuppressants used after KT, the efficacy and safety of some DAA combinations in patients with severe CKD and the worsening prognosis of CKD patients with HCV, may encourage clinicians to treat HCV patients with CKD as soon as possible, i.e. before kidney transplantation. On the other hand, there is a possibility of treating after kidney transplantation when the use of organs from HCV positive donors is a common practice.

In summary, many studies support the strong association between HCV and CKD, by reporting (i) an increased HCV infection prevalence in patients on hemodialysis, (ii) an increased incidence of CKD in HCV infected patients, and (iii) membranoproliferative glomerulonephritis secondary to HCV cryoglobulinemia vasculitis. In addition, HCV seropositivity is associated to increased risk for all-cause and cardiovascular mortality in dialysis population. It is linked to lower patient and graft survival after kidney transplantation. The recent emergence of new direct acting IFN-free antivirals, enabling high cure rates even in patients with severe renal impairment with a satisfactory safety profile should lead in the very next future to major modifications in the screening and care of HCV infection in CKD patients.

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Table 1: Pharmacokinetic data of new direct-acting antiviral treatment in HCV patients

HD: haemodialysis, ESRD: End-Stage Renal Disease, IS: Immunosuppressants, Cyclo: Cyclosporin, Tacro: Tacrolimus, AUC: Area Under the Curve, Cmax: Concentration maximal, CKD: Chronic Kidney Disease, CYP: hepatic cytochrome.

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Drug *HCV Targets*	**Metabolism**	**Elimination**	**Regular oral daily dosage**	**Adjustment if GFR < 60 ml/min/1.73 m^2**	**Adjustment if GFR < 30 ml/min/1.73m^2 or HD**	**Ciclo/Tacro interactions**	**Pharmacokinetic data**
Sofosbuvir *NS5B*	Mainly renal, the active metabolite GS-461203 via phosphorylation is dephosphorylated into inactive metabolite GS-331007	Urine (80%) Feces (14%)	400 mg	No	Insufficient data	No	After one single dose of 400 mg, increased AUC by 171% and 451% for Sofosbuvir and GS-331007, respectively
Simeprevir *NS3/4A protease*	Hepatic	Biliary (91%) Urine (< 1%)	150 mg	No	Insufficient data	Yes, need IS blood level Not recommended with Ciclo	Increased Cmax and AUC by 34% and 62%, respectively
Daclatasvir *NS5A replication complex*	Hepatic	Feces (88%) Urine (7%)	60 mg	No	No	No	26% increased AUC in HD patients
Ledipasvir *NS5A* *(co-formulation with Sofosbuvir)*	Hepatic, minimal, not CYP450 mediated	Feces (>80%) Urine (< 1%)	90 mg	No	Insufficient data	Yes, need IS blood level	No AUC increased if normal renal function Increased AUC if GFR < 30ml/min/1.73m^2
Paritaprevir/Ritonavir/Ombitasvir/ Dasabuvir *NS3/4A protease/HIV protease/NS5A polymerase*	Hepatic	Feces (>86%) Urine (2-11%)	75 mg/50 mg/25 mg/500 mg	No	No, if GFR 15-30 ml/min/1.73m^2 Caution for ESRD or HD	Yes, need to decrease IS dose	Increased AUC by 45% and 144% for paritaprevir and ritonavir, respectively
Grazoprevir/Elbasvir *NS3/4A protease/ NS5A*	Hepatic (CYP3A)	Urine < 1% for both drugs	100 mg/50 mg	No	No	Yes, Not recommended with Ciclo. Increased Tacro AUC	Increased AUC by 46% and 40% for GZR and EBR, respectively. In HD patients, increased AUC by 25% and 10% for GZR and EBR, respectively.

Table 2: Main studies evaluating interferon-free regimen in HCV patients with chronic kidney disease

Authors	Date	Design	Patients number	Genotype 1	No previous HCV treatment	Cirrhosis	Extrahepatic manifestations	Degree of CKD
Roth [65]	2015	Multicentre, phase 3, double bind, randomised	235	All	80.4%	6%	Cryoglobulinemia 1.7%	All stage 4-5, 76% HD
Hundemer [90]	2015	Retrospective case series	6	All	50%	50%	MPGN (n=1)	GFR <30ml/min (67%) or HD (33%)
Nazario [57]	2015	Retrospective case series	17	All	82%	47%	NA	GFR<30ml/min (12%) or HD (88%)
Kamar[67]	2015	Retrospective cohort	25	76%	NA	44%	MPGN (n=7), cryoglobulinemia + proteinuria (n=6), cryoglobulinemia (n=1)	KTR
Bhamidimarri[58]	2015	Open label study	15	all	40%	60%	NA	All GFR<15ml/min, 80% HD
Saxena [60]	2016	Longitudinal observational study	73	72%	47%	64%	NA	GFR 31-45ml/min (68.5%), GFR <30ml/min (24.5%), or HD (7%)
Singh [91]	2016	Retrospective case series	8	74%	88%	37%	NA	HD
Toyoda [63]	2016	Case-control study	28	All	NA	NA	NA	HD
Pockros [64]	2016	Prospective, single-arm, multicenter study	20	All	0%	0%	NA	Stage 4 (30%) or 5 (70%)
Desnoyer [56]	2016	Multicenter, prospective, observational study	12	11	50%	83%	NA	HD
Sawinski[66]	2016	Retrospective cohort	20	88%	40%	50%	NA	KTR

Authors	Treatment	Duration (weeks)	SVR12	Drug related AE	Drug-related SAE	Drug related-treatment discontinuation	Main AE
Roth	GRZ + EBR	12	99%	34%	0%	0%	Headache, nausea and fatigue
Hundemer	SOF+ SIM (50%) SOF + RBV (33%) SOF + RBV + PEG (17%)	12 (n=4), or 24 (n=2)	67%	50%	33%	17%	Anemia, leukopenia, lupus like immune renal disease
Nazario	SOF+ SIM	12	100%	24%	6%	0%	Insomnia, headache, nausea, anemia requiring blood transfusion
Kamar	SOF + SIM (n=6), or SOF + LEDI (n=9), or SOF + DACLA (n=4) or SOF +RBV (n=3) or SOF+ LEDI+ RBV (n=1) or SOF+ SIM+ RBV (n=1) or PEG+SOF+RBV (n=1)	12 (n=19), or 24 (n=6)	100%	0%	0%	0%	NA
Bhamidimarri	SOF 200mg once daily (n=11) or SOF 400mg 3 times a week (n=4)+ SIM (150mg)	12 (n=14) or 24 (n=1)	87%	ND	0%	0%	Fatigue (20%), rash/itching (13%), anemia (13%), diarrhea and loss of appetite (7%)
Saxena	SOF + SIM (40%) or SOF+RBV (30%) or SOF+PEG+RBV (18%) or SOF+SIM+RBV (11%)	NA	83%	ND	22%	4%	Fatigue, headache, nausea, anemia, worsening renal function (n=11)
Singh	SOF + SIM (50%) or SOF + LEDI (50%)	12	100%	50%	13%	0%	Nausea, vomiting, pruritus, headache, anemia
Toyoda	DACLA + asunaprevir	24	100%	21%	4%	4%	Increased ALT
Pockros	ombitasvir + paritaprevir + ritonavir + dasabuvir plus ribavirin	12	90%	50%	0%	0%	Anemia, fatigue, diarrhea, nausea, headaches
Desnoyers	SOF 400mg once daily (n=7), or SOF 400mg 3 times a week (n=5)	12 (n=7), or 24 (n=5)	83%	67%	0%	0%	Anemia, headaches, cough, anxiety, asthenia
Sawinski	SOF + SIM (n=9) or SOF+ LEDI (n=7) or SOF+RBV(n=3) or SOF+DACLA	12	100%	30%	5%	0%	Anemia requiring blood transfusion, increased creatinemia (n=4)*

(Studies or case-series with sample size>5).

HCV: hepatitis C virus, CKD: Chronic kidney disease, MPGN: membranoproliferative glomerulonephritis, GFR: Glomerular Filtration Rate, KTR: kidney transplant recipient, HD: haemodialysis, GZR: grazoprevir, EBR: elbasvir, SOF: Sofosbuvir, DACLA: Daclatasvir, LEDI: Ledipasvir, RBV: Ribavirin, SIM: Simeprevir, ALT: alanine aminotransferase, SVR12: sustained virological response week12 posttreatment, AE: adverse event, SAE: severe adverse event, NA: not available.*****attributed to supratherapeutic tacrolimus levels in 2 (resolution with tacrolimus dose reduction), uptitration of diuretics in 1 and initiation of losartan in 1 patient