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Hepatitis C and kidney disease: An overview and approach to management

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Abstract

Hepatitis C infection and chronic kidney disease are major health burden worldwide. Hepatitis C infection is associated with a wide range of extra-hepatic manifestations in various organs including the kidneys. A strong association between hepatitis C and chronic kidney disease has come to light. Hemodialysis in supporting the end stage renal disease patients unfortunately carries a risk for hepatitis C infection. Despite much improvement in the care of this group of patients, the prevalence of hepatitis C infection in hemodialysis patients is still higher than the general population. Hepatitis C infection has a negative effect on the survival of hemodialysis and renal transplant patients. Treatment of hepatitis C in end stage renal disease patients using conventional or pegylated interferon with or without ribavirin remains a clinical challenge with low response rate, high dropout rate due to poor tolerability and many unmet needs. The approval of new direct acting antiviral agents for hepatitis C may dramatically change the treatment approach in hepatitis C infected patients with mild to moderate renal impairment. However it remains to be confirmed if the newer Hepatitis C therapies are safe in individuals with severe renal impairment. This review article discusses the relationship between hepatitis C and chronic kidney disease, describe the various types of renal diseases associated with hepatitis C and the newer as well as the existing treatments for hepatitis C in the context of this subpopulation of hepatitis C patients.

Key words: Chronic hepatitis C; Kidney disease; Management

Core tip: There is a strong association between hepatitis C virus (HCV) infection and chronic kidney disease with negative impact on survival in hemodialysis and post renal transplant HCV infected patients. Recent data showed that treatment of HCV improves outcomes. In HCV infected diabetics, effective anti-HCV treatment reduces the incidence of end stage renal disease. There are now major advances in HCV treatment which may dramatically change the treatment approach in hepatitis

C infected patients.

INTRODUCTION

There are approximately 130-150 million people infected with hepatitis C virus (HCV) while the prevalence of chronic kidney disease (CKD) is between 10%-16% worldwide[1,2]. The prevalence of HCV positive among hemodialysis patients can vary from < 5% to as high as 60% from different regions in the world[3,4]. The link between HCV infection and kidney disease is well recognized[5,6]. In a large population-based study in Taiwan, the prevalence of CKD among those who are seropositive for hepatitis C was 16.5% and chronic hepatitis C infection was found to be an independent risk factor for development of CKD[5,7]. In another study, the presence of anti-HCV antibody is associated with renal disease progression with a higher rate of positive anti-HCV in those with more severe stages of CKD[8].

The survival of HCV-infected CKD patients at stage 1 and 2 CKD is thought to be similar to the non-uremic HCV patients[9]. In contrast, a meta-analysis reported negative impact of anti-HCV positivity on survival in hemodialysis patients; the adjusted relative risks for all-cause mortality was 1.35 (95%CI: 1.25-1.47) and for liver disease related mortality was 3.82 (95%CI: 1.92-7.61)[10].

The treatment for hepatitis C is rapidly evolving with many new agents in the pipeline either in late phases of development or awaiting approval. Direct acting anti-virals (DAAs) target various parts of the HCV lifecycle. In 2011, two new DAAs, the first generation of HCV-NS3/NS4A serine protease inhibitors (PI) telaprevir and boceprevir were approved for treatment of genotype 1 HCV. Two more DAAs were approved more recently; sofosbuvir, a nucleotide analog NS5B polymerase inhibitor which is effective against HCV genotypes 1, 2, 3 and 4 and simeprevir, the third NS3/NS4Aprotease inhibitor approved is effective against HCV genotype 1[11]. The newer generation of DAAs are associated with increased sustained viral response and good safety profiles.

This review describes the various types of clinical manifestations of HCV in patients with CKD and their management, which remains challenging with many unmet needs.

HEPATITIS C RESULTING IN KIDNEY DISEASE

HCV primarily affects the liver causing hepatitis; chronic hepatitis may progress to liver fibrosis and subsequently cirrhosis and hepatocellular carcinoma, which are the major burden of disease in people living with chronic hepatitis C. However, there are also extra-hepatic manifestations of HCV which include glomerulonephritis, thyroiditis, insulin resistance, diabetes mellitus, porphyria cutanea tarda, lichen planus, vitiligo, seronegative arthritis, cryoglobulinemia and lymphoproliferative disorders[6]. It has been reported that approximately 40% of the HCV infected patients have at least one extra-hepatic manifestation[12].

Large-scale community observational studies and others showed that HCV infection carries a risk for CKD and end stage renal disease (ESRD)[5,7,8,13]. Similarly in CKD patients, HCV infection increases the risk of developing ESRD with an estimated 5-year cumulative incidence rate of 52.6% compared to 38.4% in those without HCV infection[14]. This study also reported that HCV infection is an independent risk factor for developing ESRD[14]. The risk for CKD is higher in HCV patients with other co-morbidities such as diabetes, hyperlipidemia, cirrhosis, male gender, age < 50 years, and those on more than 6 years follow-up for HCV[7].

Several factors may contribute to the development of ESRD in HCV infected patients. HCV may trigger a cascade of immune reactions that subsequently attack the kidneys and result in glomerulonephritis. HCV was also found to be associated with insulin resistance and dyslipidemia[15], thus, indirectly increasing the risk of renal disease.

Kidney diseases associated with HCV may present clinically as nephritic, nephrotic syndrome or isolated proteinuria with or without impairment in renal function. The pathological changes on renal biopsy are membranoproliferative glomerulonephritis (MPGN), membranous glomerulopathy (MG), IgA nephropathy, focal segmental glomerulosclerosis, mesangial proliferative glomerular nephritis or tubulointerstitial nephritis[16]. In an Italian multi-centre study of 146 cryoglobulinemic glomerulonephritis, 87% was HCV infected[17]. Diffuse MPGN was the most common renal biopsy finding in 83% of patients and type Ⅱ cryoglobulin was detected in 74.4% of cases.

In a case-control study, it was also found that MPGN was significantly more prevalent than membranous glomerulopathy among HCV associated kidney disease patients (0.36% *vs* 0.05%; *P* < 0.0001), with the most common involvement being type I MPGN associated with type Ⅱ mixed cryoglobulinemia[6].

Glomerulonephritis may occur many years or even decades after HCV infection. The mechanism for MPGN related to HCV is thought to be immune-complex mediated (antigen-antibody immune complexes formation from chronic infection) and these immune complexes activate the classical pathway of complements and cause deposition of immunoglobulins, complement factors and both kappa and lambda light chains in the mesangium and the capillary walls[18]. HCV-NS3 viral antigen deposits were detected in kidney tissues of patients with positive HCV

RNA and MPGN[19,20]. Cryoglobulins are immunoglobulins which become insoluble at below body temperature and dissolve when rewarmed. In individuals with HCV infection, these cryoglobulins are immune complexes formed by monoclonal immunoglobulin M (usually IgM Rheumatoid factor), polyclonal immunoglobulin G and HCV RNA which are deposited in the small and medium-sized vessels of the skin, kidneys and peripheral nerves. The deposition of these immune complexes in the mesangium of the kidneys triggers glomerulonephritis. Although proteinuria below nephrotic range, microscopic hematuria, mild to moderate renal insufficiency and arterial hypertension are among the classical clinical features, 30% of chronic hepatitis C with cryoglobulinemia have non-specific features like purpura, asthenia and arthralgia. Less than 10% have vasculitis affecting the kidney, skin and nerves[21,22]. Alanine transaminases are raised in 70% of patients, complements like C4, C1q are very low while C3 is only slightly low and the majority are rheumatoid factor positive[21,23]. Patients with diffuse MPGN showed higher levels of proteinuria and lower C4 levels[17]. The clinical course of patients with MPGN and cryoglobulinemia is classically relapsing and remitting, the top three causes of death are cardiovascular, sepsis and liver failure[17]. ESRD requiring hemodialysis is infrequent due to early mortality during the course of CKD before approaching ESRD[17,23].

Interestingly, studies also found an association of occult HCV in immune-mediated glomerular nephropathies[24,25]. In these studies, occult HCV is defined as negative anti-HCV-antibodies and serum HCV RNA but presence of HCV RNA in mononuclear cells in peripheral blood or in serum after ultra-centrifugation or HCV antigen detection using immuno-histochemistry in frozen renal tissues. The clinical implication of this finding requires further studies.

In the management of HCV-infected individuals, it is imperative that clinicians actively screen for kidney disease and prevent or control the additional risk factors (diabetes, hyperlipidemia and cirrhosis) for CKD. The liver and renal clinical practice guidelines recommend annual surveillance for hematuria and proteinuria in HCV-infected patients for early detection of glomerulopathies[9,26].

HEPATITIS C AND HEMODIALYSIS

In 2004, the Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that 13.5% of hemodialysis patients are infected with hepatitis C. The prevalence rates of hepatitis C among these patients exhibits regional variations with less than 5% in the United Kingdom and Germany and higher prevalence of more than 20% in Spain and Italy[27]. Among 10 countries studied within the Asia-Pacific region, the HCV seroprevalence among hemodialysis patients were between 0.7% and 18.1%[28]. In addition, the prevalence of HCV were higher in HD group compared to patients on peritoneal dialysis [(7.9% ± 5.5%) *vs* (3.0% ± 2.0%), $P = 0.01$]. More importantly, the prevalence of HCV patients with ESRD who underwent hemodialysis can be at least five times higher compared to the general population[3,9,29,30].

There are mainly two groups of HCV infected patients in the hemodialysis unit, either the patients already have HCV infection before entering into treatment with hemodialysis or the HCV infection was acquired during the maintenance hemodialysis. The mode of HCV transmission is parenteral through contaminations from surfaces, supplies, invasive procedures, direct contact among patients and from breach in infection control practices[9]. Before the era of screening blood donors for HCV and the use of erythropoetin, multiple blood transfusions to treat anemia in dialysis patients had contributed to the increased prevalence of HCV transmission[3]. In one prospective observational study conducted in three major continents, the prevalence of HCV in hemodialysis patients were higher among those who were on dialysis for longer duration, male gender, black ethnicity, concurrent illness like diabetes or hepatitis B infection, prior kidney transplant and alcohol or substance abuse[27]. In its guideline to prevent HCV transmission in hemodialysis unit, Kidney Disease Improving Global Outcome (KDIGO) guidelines stressed the importance of compliance to strict infection-control procedures at all times[9].

A meta-analysis on patients receiving maintenance hemodialysis, found that HCV-positive patients have higher mortality compared to HCV-negative patients. This study showed that liver-related death was higher than cardiovascular-related death among these groups [adjusted relative risk 3.82 (95%CI: 1.92; 7.61) *vs* 1.26 (95%CI: 1.10; 1.45) respectively][10]. Deaths due to hepatocellular carcinoma and liver cirrhosis was higher in HCV-positive group[31]. There is no observed difference between hemodialysis and peritoneal dialysis on the survival rate of these HCV infected dialysis dependent patients[32,33].

HEPATITIS C AND RENAL TRANSPLANT

Hemodialysis is a risk factor for HCV infection. KDIGO guidelines recommend all renal transplant candidates should be screened for HCV and state that HCV infection is not a contraindication to renal transplant. A meta-analysis on 13 observational studies by Fabrizi *et al*[34] found that most studies showed an increase in all-cause mortality and all-cause renal graft loss among renal transplant recipients with HCV[34]. This is likely due to post-transplant immunosuppression and undiagnosed HCV infection prior to transplant. Hepatitis C infection in the setting of post renal transplant had been reported to cause specific diseases in the liver and the transplanted kidney.

In a cohort study of 614 renal transplant recipients, 2.45% (15 recipients) were diagnosed with MG post transplant. In eleven of them were *de novo* MG and 6 out of the 11 *de novo* MG cases were associated with HCV infection. All but one of the HCV infected recipients were not treated before the transplant[35]. Other studies

also found that HCV is a strong aetiologic factor for development of MG post transplant[36,37].

Fibrosing cholestatic hepatitis had been reported in HCV-infected renal transplant recipients. It is a complication of immunosuppression resulting in extremely high serum HCV RNA levels causing rapid progression to liver failure, sepsis and associated with high mortality rates. Biochemical profiles showed progressive cholestatic jaundice with liver biopsy showing characteristic features of cholestasis and fibrosis. Withdrawal or reductions of immunosuppression tend to have significant impact on preventing the progression of liver failure[38,39] but at the expense of possible renal graft loss.

In a study by de Oliveira Uehara *et al*[40], 22 renal transplant recipients who were HCV-positive and have pre and post transplant liver biopsies, were followed up to 7 years post transplant. Fifty percent of the patients showed progression in liver fibrosis and 32% had worsening of liver necro-inflammatory activity. Post transplant worsening of liver fibrosis was also detected in patients with no histological changes prior to the transplant[40]. In another study by Roth *et al*[41], 44 patients with HCV-positive recipients were followed for slightly shorter interval showed no significant liver disease progression, 16% of the studied recipients showed histologic improvement, and 23% showed progression of liver disease[41]. It is likely that HCV infection post renal transplant will gradually cause worsening of liver disease in the majority of cases.

A prospective study showed that despite significant decrease in patient and renal graft survival post renal transplant in HCV positive recipients compared to their HCV negative counterparts, the survival of HCV positive ESRD is still better with renal transplant rather than remaining on maintenance hemodialysis[42]. Kidneys from anti-HCV positive donors have been used to transplant HCV infected renal recipients[43]. This approach will help to shorten the waiting time for HCV RNA positive renal transplant candidates[44,45]. In addition to the benefit of shorter waiting time, the use of kidneys from HCV positive donors had also been shown to improve the overall survival compared to staying on the waiting list (adjusted HR for death 0.76, 95%CI: 0.60, 0.96)[46]. However, transmission from infected donor may produce super-infection from a different HCV genotype[47].

ASSESSMENT OF HEPATITIS C AND LIVER DISEASE STATUS IN RENAL PATIENTS

The clinical tools used in assessing HCV and the liver disease in non-uremic patients are generally applicable to renal patients apart from a few notable differences. HCV infected patient on hemodialysis tend to have normal alanine transaminase possibly due to high lactate level, which cause rapid consumption of NADH co-enzyme or enzyme during dialysis[48].

All anti-HCV-positive CKD patients should be assessed

for HCV RNA viral load, HCV genotyping as well as liver fibrosis. HCV genotype is a strong predictor of response to anti-HCV treatment. KDIGO recommended special steps in drawing blood sample for HCV RNA tests in hemodialysis patients because heparin is an inhibitor of polymerase chain reaction[49]. In order to avoid contamination with heparin which is used in hemodialysis session, the blood sample for HCV RNA should be taken from a peripheral vein before the dialysis session[9].

Assessment of severity of liver disease is recommended prior to anti-HCV therapy. KDIGO recommend that HCV-infected potential kidney transplant candidates to undergo liver biopsy as part of the pre-transplant assessment. In a study which had 284 HCV infected hemodialysis patients undergoing liver biopsies, the complications reported were local pain in 18.3%, shoulder soreness in 11.7%, oozing at puncture site in 11.3%, liver hematoma in 1.1% and only one patient suffered from hemoperitoneum[50]. Another study on percutaneous liver biopsy in chronic hepatitis C patient with or without renal failure also found the procedure to be safe without any increased risk in hepatitis C infected ESRD[51].

We look into several studies that analysed liver biopsy findings in this group of patients. These studies revealed that about 22%-81% of HCV positive ESRD patients had histological evidence of liver fibrosis on biopsy while a smaller percentage of approximately 13%-25% had biopsy proven cirrhosis[52-54].

Although serious complications of liver biopsy are uncommon, the procedure is not well accepted by patients, and is open to sampling as well as interpretation errors. Non-invasive methods to evaluate the severity of liver disease in management of hepatitis C patients have been recommended[26,55]. A combination of non-invasive tests improves the diagnostic accuracy. An easily available method for assessing liver fibrosis in HCV patients is by using amino transaminase-to-platelet ratio index (APRI). APRI is calculated by [(amino-transaminase/upper limit normal)/platelet count $(10^9/L)] \times 100$. A study in HCV infected ESRD patients found that APRI > 0.4 and < 0.95 can correctly predict 50% patients with F3-F4 fibrosis, 33% of F3-F4 fibrosis patients may have been mislabeled and consequently did not have a liver biopsy as part of the renal transplant assessment. The authors concluded that APRI was not a good predictor of hepatic fibrosis in transplant evaluation of HCV-positive ESRD patients[56]. An earlier study showed that APRI is a precise and reproducible test in predicting hepatic fibrosis in hemodialysis patients[57]. The different findings in these two studies were probably due to the different cut-off values used in predicting fibrosis.

Transient elastography (TE) has been found to be superior to APRI in assessing the severity of liver fibrosis especially in hemodialysis HCV infected patients with significant liver fibrosis ($\geqslant$ F2 and $\geqslant$ F3)[50]. Overnight fasting before TE measurement is recommended to minimize the effect of raised portal and central venous pressure. The optimal cut off values were 5.3 kPa, 8.3 kPa and 9.2 kPa for fibrosis stage $\geqslant$ F2, $\geqslant$ F3 and F4,

respectively. It is noteworthy that a systematic review of 12 studies showed that TE is an excellent tool to identify HCV-related cirrhosis but not accurate for early stages of liver damage[58].

Patients with clinical or histological evidence of cirrhosis should have further assessments to look for the complications of cirrhosis such as upper endoscopy for varices and liver ultrasound for hepatocellular carcinoma surveillance.

TREATING HEPATITIS C INFECTION IN CKD PATIENTS

KDIGO recommends that all CKD patients with HCV infection to be assessed for anti-HCV therapy. As there are risks of interferon (IFN) therapy and benefits of avoiding the complications related to HCV infection in post renal transplant setting, KDIGO and other liver guidelines state that HCV infected renal transplant candidates should be treated for hepatitis C before renal transplant[9,26]. In clinical practice, the decision to treat HCV infection in a patient with CKD must be individualized after discussion of the potential risks and benefits of therapy. Factors such as life expectancy, renal transplant candidacy, other co-morbidities and the available expertise should be taken into consideration[9,26,55]. CKD patients in Stages 1 and 2 have normal survival as in the general population but CKD stage 3 and 4 have lower 5 years survival at 76% and 54% respectively. However the survival of CKD stage 5 patients is markedly diminished compared to the general population without renal impairment[9]. The liver-related complications of HCV, namely cirrhosis and hepatocellular carcinoma, have been implicated in the lower survival of HCV infected CKD Stage 5D or hemodialysis patients[31].

The widely accepted standard of care (SoC) for HCV therapy is pegylated IFN (PegIFN) in combination with ribavirin[26]. Using this SoC in renal impaired patients has several limitations mainly due to aggravated side effects resulting in premature discontinuation of therapy, higher dropout rates and treatment related mortality. Consequently, only few HCV-infected kidney disease requiring hemodialysis patients are treated. DOPPS reported that 4735 out of 49762 patients on hemodialysis were HCV-positive (9.5%) but only 48 out of 4589 (1%) patients with prescription data receive anti-viral treatment[59]. In the same study, among 617 HCV-positive renal transplant candidates, only 3.7% receive anti-viral treatment. Nevertheless, HCV-positive dialysis patients who received treatment were found to have better survival than untreated group.

CKD patients mostly suffer from multiple co-morbidities. Diabetes mellitus, hypertension and cardiovascular disease are among the co-morbidities that reduce the survival rate among CKD patients but also render them poor candidates for the current SoC anti-HCV therapy. Management of HCV-infection in kidney disease patients with multiple co-morbidities remains a challenge.

Renal transplant candidates with HCV-infection are recommended to receive HCV treatment due to benefits in slowing the development of liver disease and reduce the risk of HCV-related post-transplant complications[41] such as new-onset diabetes mellitus[60] and chronic allograft nephropathy[61]. In a controlled clinical trial by Cruzado *et al*[62], renal transplant recipients who received pre-transplant IFN therapy were shown to have a significantly lower rate of *de novo* glomerulonephritis compared to recipients who were untreated[62].

The objective of anti-HCV treatment is to achieve sustained virological response (SVR), which is classically defined as undetectable HCV RNA by polymerase chain reaction at 6 mo after interferon-based treatment. Achieving SVR in advanced fibrosis patients is associated with a decrease in all cause mortality, reduce risk of liver transplantation as well as liver related deaths like liver failure and hepatocellular[63]. However the benefits span beyond the liver. A Taiwan population based cohort study stratified diabetes mellitus patients into 3 groups; HCV-infected patients who were treated with PegIFN and ribavirin, HCV-infected patients who were never treated and an uninfected group. The 8-year cumulative incidence of ESRD and acute coronary syndrome were significantly lower in those who received anti-HCV therapy[64]. The authors concluded that treatment of HCV-infected patients with PegIFN and ribavirin was associated with improvements in cardiovascular and renal outcomes in diabetes mellitus patients.

Moreover, a meta-analysis on the durability of SVR in successfully treated HCV showed 86% durability in those who remained on maintenance hemodialysis while in those who received renal transplant it was 95% durable after a follow-up of 48 mo[65].

APPROVED ANTI-HCV THERAPIES AND THEIR USE IN RENAL IMPAIRMENT

IFN is broken down mainly in the kidneys therefore IFN therapy in patients with kidney disease may result in a significant amount of IFN accumulation in the body. PegIFN was introduced where the polyethylene glycol is attached to the IFN molecule making it more stable and longer half-life in the plasma. Instead of thrice weekly IFN injection, PegIFN requires only weekly injection. The two formulations of pegylated interferon are PegIFN-α2a and PegIFN-α2b. The latter is weight based at 1.5 mcg/kg while PegIFN-α2a dose is 180 mcg regardless of body weight. PegIFN-α2a is metabolized in both the kidneys and liver while PegIFN-α2b only by the kidneys. Plasma concentration of PegIFN is significantly elevated in hemodialysis patients, thus, PegIFN dose has to be reduced. For patients with creatinine clearance (CrCl) of < 30 mL/min and on hemodialysis, PegIFN-α2a dose should be reduced from 180 mcg to 135 mcg weekly[66]. PegIFN-α2b dose should be reduced by 25% in patients with CrCl of 30-50 mL/min, and by 50% in patients with

CrCl of < 30 mL/min or on hemodialysis[67].

Ribavirin is a nucleoside analogue that when combined with PegIFN increases the rates of SVR. Ribavirin can accumulate in the red blood cells and may lead to hemolytic anemia due to the lack of phosphatase. Toxicity increases significantly with impaired CrCl as its plasma concentration increase when the CrCl is < 50 mL/min. Measuring plasma levels of ribavirin is not a widely available clinical tool. Studies have shown that ribavirin 200 mg or 400 mg on alternate days to be reasonably well tolerated by patients with moderate renal impairment, while in patients with severe renal impairment or on dialysis ribavirin 200 mg daily can be used[68]. Using low-dose ribavirin in CKD patients need more frequent monitoring of hemoglobin[69,70].

Boceprevir selectively inhibits NS3 serine protease, which is vital for HCV RNA replication into virions inside the host cells[71]. In phase 3 clinical trials, boceprevir combined with PegIFN and ribavirin in HCV genotype 1 achieved SVR of 60% for treatment naïve HCV patients, and 63% SVR for relapsers and previous partial responders[72,73]. A study by Treitel *et al*[74] showed no significant pharmacokinetic changes in patients with liver and renal impairments. The authors suggest that boceprevir dose modification is not necessary in patients on dialysis[74].

Telaprevir in combination with PegIFN and ribavirin achieved up to 75% SVR in treatment naïve HCV Genotype 1 patients, while in previous relapsers, partial responders and null responders the SVR were up to 88%, 59% and 33% respectively, *vs* 24%, 15% and 5% in the PegIFN/ribavirin arm[75]. Telaprevir plasma concentration increase by 21% in patients with renal impairment compared to normal renal functions[76]. According to the package insert, telaprevir does not require any dose adjustment in patients with mild, moderate or severe renal impairment[77].

A recent study by Mauss *et al*[78], reported that 4.7% patients on boceprevir and 6.6% patients on telaprevir experienced reduction in estimated glomerular filtration rate (eGFR) to < 60 mL/min compared to 0.9% in the PegIFN and ribavirin only group ($P < 0.05$). Several factors contributing to the reduction in GFR were older age ($P < 0.001$), hypertension ($P < 0.05$), higher serum baseline creatinine ($P < 0.001$) and being on triple therapy PegIFN/ribavirin with boceprevir or telaprevir ($P < 0.01$)[78]. Similar findings were also reported in other studies[79,80].

Simeprevir together with PegIFN plus ribavirin in phase III studies achieved SVR rates of 80% and in treatment naïve HCV genotype 1 patients and previous relapsers to PegIFN/ribavirin compared to 36.1% in PegIFN/ribavirin group[81]. No dose adjustment is needed in mild, moderate or severe renal impairment but the data on simeprevir in ESRD or dialysis patients is lacking[82].

In treatment naïve HCV genotype 1, sofosbuvir with PegIFN plus ribavirin therapy for 12 wk achieved SVR up to 89%[83]. With the approval of sofosbuvir and ribavirin, interferon free regimen is now available for genotype 2 and 3 patients. For genotype 2 HCV patients, sofosbuvir with ribavirin for 12 wk yielded 95%-97% SVR in treatment naïve patients and 82%-90% SVR rate in previously treated patients. In HCV genotype 3 patients, sofosbuvir with ribavirin for 24 wk produced SVR rate of 93% in treatment naïve and 77% in previously treated patients[83,84]. No dose adjustment is required in renal impaired patients. However, sofosbuvir package insert does not recommend the use of this drug in those with severe renal impairment or ESRD due to higher exposures of the predominant sofosbuvir metabolite[85]. EASL and AASLD/IDSA/IAS-USA2014 guidelines on HCV treatment do not recommend sofosbuvir in patients with eGFR of < 30 mL/min per 1.73 m^2 or with ESRD until more data are available[55,86].

Apart from the above, there are also specific restrictions on co-administration of certain drug categories with each of DAAs mentioned above which may affect the plasma levels of these DAAs. For instance, sofosbuvir co-administration with drugs which induce P-glycoprotein like rifampin, carbamazepine, phenytoin or St. John's wort are not allowed[85]. In the case of simeprevir, dose adjustments are needed with some medications that are commonly prescribed in CKD patients like anti-arrhythmics, warfarin, calcium channel blockers, antibiotics, antifungals and 3-hydroxy-3-methyl-glutaryl-Co-A reductase inhibitors[82]. As CKD patients are likely to be prescribed various medications for their co-morbidities, taking a good medication history and checking for drug-drug interactions are important steps before initiating treatment with DAAs.

Table 1 shows a summary of recommendations on HCV therapy in various stages of renal impairment according to the various guidelines. A summary of systematic reviews on the treatment of HCV in patients with renal disease is shown in Table 2.

TREATMENT FOR HEPATITIS C RELATED GLOMERULONEPHRITIS

In the current understanding of HCV related glomerulonephritis (GN), HCV is the infectious agent which cause GN. The renal disease shows injury from immune complex deposition and cryoglobulins. According to the recent AASLD/IDSA/IAS-USA hepatitis C guideline, HCV patients with type 2 or 3 essential mixed cryoglobulinemia and end-organ manifestations (*e.g.*, vasculitis), proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis are included in the highest priority for anti-HCV treatment due to the high risk for severe complications[87]. Progressive renal disease, proteinuria to the extent of nephrotic syndrome and hypertension are the main manifestations of GN. Therefore a multi-prong approach to the management of HCV related GN involves controlling the clinical manifestations and protecting the kidneys, eradicating HCV, and also reducing the formation and deposition of HCV containing immune complexes in the glomeruli. Anti-hypertensive and anti-proteinuric

Table 1 Summary of recommendations on hepatitis C virus therapy in various stages of renal impairment according to guidelines

CKD stage	KDIGO 2008	APASL 2012	EASL 2014	AASLD/IDSA/IAS-USA 2014
Stage 1 and 2 Stage 1 = GFR ≥ 90 mL/min per 1.73 m^2 Stage 2 = GFR 60-89 mL/min per 1.73 m^2	PegIFN and ribavirin Dose of ribavirin to be titrated to patient's tolerance	PegIFN and ribavirin		PegIFN and ribavirin/sofosbuvir/simeprevir Dose of: (1) PegIFN 2a is 180 µg/wk (2) PegIFN 2b is 1.5 µg/kg per week (3) Ribavirin is 1000 mg or 1200 mg if body weight < 75 kg or ≥ 75 kg (4) Sofosbuvir is 400 mg daily (5) Simeprevir is 150 mg daily
Stage 3, 4 and 5 Stage 3 = GFR 30-59 mL/min per 1.73 m^2 Stage 4 = GFR 15-29 mL/min per 1.73 m^2 Stage 5 = GFR < 15 mL/min per 1.73 m^2	PegIFN Dose of PegIFN to be adjusted to renal function	PegIFN and ribavirin Dose of: (1) PegIFN 2a is 135 µg/wk (2) PegIFN 2b is 1 µg/kg per week (3) Ribavirin is 200-800 mg/d		For GFR = 30-50 mL/min per 1.73 m^2 PegIFN and ribavirin/sofosbuvir/simeprevir Dose of: (1) PegIFN 2a is 180 µg/wk (2) PegIFN 2b is 1 µg/kg per week or 25% reduction (3) Ribavirin is alternating doses 200 and 400 mg every other day (4) Sofosbuvir is 400 mg daily (5) Simeprevir is 150 mg daily For GFR < 30 mL/min per 1.73 m^2 PegIFN and ribavirin/simeprevir Dose of: (1) PegIFN 2a is 135 µg/wk (2) PegIFN 2b is 1 µg/kg per week or 50% reduction (3) Ribavirin is 200 mg daily (4) Simeprevir is 150 mg daily
Stage 5D GFR < 15 mL/min per 1.73 m^2 on maintenance hemodialysis	Conventional IFN Dose to be adjusted to a GFR < 15 mL/min per 1.73 m^2	Conventional IFN or PegIFN and markedly reduced dose of ribavirin Dose of: (1) PegIFN 2a is 135 µg/wk (2) PegIFN 2b is 1 µg/kg per week	IFN free and if possible ribavirin free but no safety and efficacy data	PegIFN or conventional IFN and ribavirin Dose of: (1) PegIFN 2a is 135 µg/wk (2) PegIFN 2b is 1 µg/kg per week (3) Conventional IFN is 3 mU 3 x/wk (4) Ribavirin is 200 mg/d

CKD: Chronic kidney disease; KDIGO: Kidney Disease Improving Global Outcome; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Disease; IDSA: Infectious Disease Society of America; IAS-USA: International Antiviral Society-United States of America; PegIFN: Pegylated interferon; IFN: Interferon; GFR: Glomerular filtration rate; KDIGO 2008: Patients with genotypes 1 or 4 is for 48 wk of therapy if an early virological response (EVR) is obtained at 12 wk (> 2 log fall in viral titer). Genotype 2 or 3 is for 24 wk[9]. APASL 2012: Patients with genotypes 1 is for 48 wk treatment if achieve a complete EVR at week 12, if achieved rapid virological response (HCV RNA undetectable) at week 4 and HCV RNA at baseline is < 400000 IU/mL for shorten treatment to 24 wk and if not achieve an EVR at week 12, but show a significant reduction in HCV RNA levels (partial EVR) and negativity of HCV RNA at week 24 (late virological response, LVR), treatment may be continued up to 72 wk. For Genotype 2 or 3 is 24 wk treatment[26]. EASL 2014: Regimens for patients with genotype 1 are 12 wk of sofosbuvir/ribavirin/PegIFN or 12 wk of sofosbuvir/simeprevir/ribavirin or 24 wk of sofosbuvir/ribavirin. For genotype 2 is 12 wk of sofosbuvir/ribavirin. For genotype 3 are 24 wk of sofosbuvir/ribavirin or 12 wk of sofosbuvir/ribavirin/PegIFN. For genotype 4 are 12 wk of sofosbuvir/ribavirin/PegIFN or 24 wk of sofosbuvir/ribavirin or 24 wk PegIFN/ribavirin/simeprevir for first 12 wk. For genotype 5 or 6 are 12 wk of sofosbuvir/ribavirin/PegIFN or 24 wk of sofosbuvir/ribavirin[55]. AASLD/IDSA/IAS-USA 2014: Regimens for patients with genotype 1 are 12 wk of sofosbuvir/ribavirin/PegIFN or 12 wk of sofosbuvir/ribavirin/simeprevir or 24 wk of PegIFN/ ribavirin/simeprevir for first 12 wk or 24 wk of sofosbuvir/ribavirin or 24 wk of sofosbuvir/simeprevir. For genotype 2 is 12 wk of sofosbuvir/ribavirin. For genotype 3 are 24 wk of sofosbuvir/ribavirin or 12 wk of sofosbuvir/ribavirin/PegIFN. For genotype 4 are 12 wk of sofosbuvir/ribavirin/PegIFN or 24 wk of sofosbuvir/ribavirin or 24-48 wk of PegIFN/ ribavirin/sofosbuvir for first 12 wk. For genotype 5 or 6 are 12 wk of sofosbuvir/ribavirin/PegIFN or 48 wk of PegIFN/ribavirin[132].

medications are reno-protective agents, which will delay progression of renal disease while anti-hyperlipidemic therapy may also be required. Diuretics administered together with angiotensin converting enzymes inhibitors and/or angiotensin receptor blockers were proven to be effective[88,89].

Data on specific treatment in HCV related GN was generally limited. Anti-viral therapies like IFN with or without ribavirin were studied in small number of clinical trials or pilot studies and the results were heterogenous. A systematic review on anti-viral therapy in symptomatic HCV-associated mixed cryoglobulinemia showed that combination therapy of PegIFN and ribavirin achieved SVR of 0.52 (95%CI: 0.40; 0.63) while conventional IFN plus ribavirin achieved SVR of 0.32 (95%CI: 0.15; 0.49)[90]. Other than anti-HCV treatment, immunosuppressive agents (cytotoxics and corticosteroids) and plasma exchange are also among the approach in treating HCV related GN. HCV related cryoglobulinemic GN is currently using a more targeted approach, which are anti-virals, B-cell depletion therapy and non-specific immunosuppressive therapy[91]. Fabrizi *et al*[92] in a recent review article on HCV-mixed cryoglobulinemia have divided treatment strategies based on clinical-biological presentation. The presentations were divided to mild to moderate disease, severe disease and life threatening[92]. Mild to moderate disease was

Table 2 Summary of systematic reviews on hepatitis C virus treatment in patients with renal disease

HCV and renal condition/ref. and year	No. of trials/patients	Types and duration of treatment	SVR	Notes
Glomerulonephritis				
Fabrizi *et al*[90] (2013)	Trials = 10	Combination of PegIFN plus ribavirin 6 mo to more than 12 mo	52%	Dropout rate = 15%
	Patients = 300	Conventional IFN plus ribavirin 6 mo to more than 12 mo	32%	
Acute Hepatitis C				
Fabrizi *et al*[116] (2012)	Trials = 8	Conventional or PegIFN	58%	Dropout rate = 9%
	Patients = 173	3 mo to 12 mo		Genotype 1 = 49%
Hemodialysis				
Fabrizi *et al*[117] (2008)	Trials = 28 Patients = 645	Conventional IFN or PegIFN	31%-39%	Dropout rate = 19%-27%
Fabrizi *et al*[118] (2010)	Trials = 16 Patients = 254	PegIFN 24-48 wk	33%-38%	Dropout rate = 23%
Fabrizi *et al*[122] (2011)	Trials = 10	Conventional interferon + ribavirin or Peg-IFN + ribavirin	56%	Dropout rate = 25%
	Patients = 151	24-48 wk		Genotype 1 = 58.3%
Renal transplant				
Wei *et al*[128] (2014)	Trials = 12	Conventional IFN monotherapy or Conventional IFN plus ribavirin or PegIFN + ribavirin	26.6% PegIFN base = 40.6%	Dropout rate = 21.1%
	Patients = 140	3.5 to 33 mo	Conventional IFN base = 20.9%	Graft rejection rates = 4%

HCV: Hepatitis C virus; SVR: Sustained viral response; IFN: Interferon; PegIFN: Pegylated interferon.

defined as no worsening nephritis, polyneuropathy or other complications. Severe disease was defined as progressive motor neuropathy, worsening nephritis and extensive skin involvement. Life-threatening disease was defined as rapidly progressing GN, central nervous system, gastrointestinal with or without respiratory involvement.

Studies on anti-viral agents used in HCV related GN were mainly explored in small observational studies. Most of these studies showed positive effects of antiviral therapy in terms of achieving SVR and clinical improvement[93-97]. In HCV-mixed cryoglobulinemia, the use of standard IFN alpha monotherapy showed high frequency of viral and clinical relapse[98,99]. Combination of IFN alpha with ribavirin has shown improvement in HCV-mixed cryoglobulinemia patients with cutaneous, kidney and neurologic manifestation[100] together with better rate of clinical and viral response[95]. In HCV-related GN, IFN alpha monotherapy was shown to improve proteinuria and HCV RNA clearance compared to immunosuppressive therapy with corticosteroids, but no significant improvement of kidney function by either treatment was observed[101]. The authors suggested that further well-designed study is needed. In a recent meta-analysis of 11 controlled and uncontrolled clinical studies on IFN-based anti-HCV therapy in CKD patients showed significantly decrease in proteinuria and stabilization of serum creatinine. Improvement in proteinuria is related to SVR but there was no association between serum creatinine and HCV RNA clearance[102].

Rituximab is an anti-CD20 monoclonal antibody which cause rapid depletions of B-cells and therefore interferes with cryoglobulins and monoclonal IgM production. In HCV-mixed cryoglobulinemia, the use of rituximab was shown to reduce proteinuria significantly[103] and achieve complete clinical response in up to 60%-70% of patients[104]. A prospective cohort study by Saadoun *et al*[97] showed that rituximab plus PegIFN and ribavirin produced better renal response rate (normalization of serum creatinine and resolution of proteinuria and/or hematuria), shorter time to clinical remission and higher rate of cryoglobulin clearance compared to PegIFN and ribavirin only therapy in HCV-mixed cryoglobulinemia patients[97]. Hence rituximab may be considered in severe or life-threatening disease.

Corticosteroids and other immunosuppressive agents like cyclophosphamide or azathioprine may be considered in life threatening HCV-mixed cryoglobulinemic vasculitis. High dose corticosteroids may induce remission during the acute stage. However, several studies that evaluated the use of immunosuppressive agents gave variable results with small success rates[23,105,106].

A problem with the use of steroids or immuno-suppressive agents is the increase in HCV replications and consequent detrimental effects on the liver. Acute exacerbation with increase in serum transaminases and HCV RNA viral load had been reported in cancer patients with chronic hepatitis C who received treatment with chemotherapy and the use of rituximab is an associated risk factor[107]. The KDIGO guideline on GN noted that cyclical corticosteroids or alkylating agents is contra-indicated in idiopathic membranous nephropathy when there is untreated infection including hepatitis C.

Plasmapheresis theoretically removes immune complexes and cryoglobulins[108]. It is usually performed during acute phase or life-threatening disease and is effective in rapidly progressive GN[109]. It may be useful in patients with poor response to anti-viral therapy or immunosuppressant.

The recent KDIGO clinical practice guideline for GN

recommended the use of PegIFN alpha plus ribavirin in patients with moderate proteinuria, stable renal functions (CKD stages 1 and 2) and mild to moderate histological changes[110]. In nephrotic range proteinuria and/or rapid progressive GN and acute flare of cryoglobulinemia, rituximab or plasmapheresis, cyclophosphamide and intravenous corticosteroids should be given[9]. Once the acute phase has resolved, IFN-alpha therapy may be initiated to prevent exacerbation of cryoglobulinemic vasculitis[111]. It is unclear how soon the anti-HCV therapy should be initiated after starting the immunosuppressive agents; further research in the optimal treatment of this group of patients is required[104].

TREATMENT FOR ACUTE HEPATITIS C IN CKD PATIENTS

Acute hepatitis C occur among CKD populations mainly due to past blood transfusions, horizontal transmissions or even from nosocomial infections in dialysis unit. This is a concern as 85%-90% of untreated acute hepatitis C progress to chronic hepatitis C[112]. Data on treatment in acute HCV infection among CKD patients is limited, partly due to the silent nature of an acute HCV infection causing difficulty in the diagnosis. Spontaneous clearance of HCV RNA in acute hepatitis C occur in 5%-30% of patients[112-114], hence, KDIGO 2008 recommended waiting for a minimum 12 wk before initiating HCV treatment in CKD patients[9]. Treatment of acute hepatitis C in hemodialysis patients with conventional IFN achieved higher rate of HCV RNA clearance compared to those not treated. Patients given high dose IFN (6-10 million units three times per week) therapy are more likely to stop therapy compared to those on low dose IFN (3 million units three times per week) due to adverse events[113]. A study on acute hepatitis C hemodialysis patients, showed high SVR rate at 88.6% in those receiving PegIFN 135 mcg once per week *vs* 16.7% spontaneous viral clearance rate in the control group[115]. A meta-analysis on treatment of acute HCV in patients on dialysis with conventional or PegIFN showed SVR rates of 58% (95%CI: 38:77) and dropout rates of 9% (95%CI: 4:14)[116]. The higher SVR rate achieved in dialysis patients with acute HCV compared to chronic HCV underscore the need to treat acute HCV infection in hemodialysis patients to reduce the risk of chronicity.

TREATMENT FOR CHRONIC HEPATITIS C IN HEMODIALYSIS PATIENTS

The higher prevalence of HCV infection in hemodialysis patients compared to the general population, as well as robust data showing increased mortality in HCV positive hemodialysis patients and renal transplants patients and the higher risk of all cause renal graft loss are some of the reasons why HCV positive hemodialysis patients need to be treated[3,9,29,30,34]. Two meta-analyses by Fabrizi *et al*[117] found that SVR rate for HCV infected hemodialysis patients treated with conventional IFN monotherapy resulted in SVR of 39% and a drop-out rate of 19%[117], while for PegIFN monotherapy the SVR was 33% and drop-out rate was 23%[118]. The adverse effects were mainly anemia and gastrointestinal symptoms. However, late side effects such as neurological and cardiovascular adverse effects were the main reasons for discontinuation of therapy. The reason for the high occurrence of side effects was probably due to altered pharmacokinetics of IFN in ESRD patients; doubling of the plasma IFN concentration-time curve was observed in ESRD patients compared to normal kidney function patients[119]. Gradual increase in the IFN-alpha is an option to improve tolerability and achieve adequate dose of treatment and consequently better SVR. Treatment with PegIFN-α2b monotherapy beginning with a dose of 0.5 μg/kg per week, and gradually increasing every 4 wk to a maximum of 1 μg/kg per week resulted in an overall SVR rate of 50% while in genotype 3 patients the SVR rate was 80%[120].

Ribavirin is mainly removed by the kidneys and there is very little elimination by hemodialysis. The use of ribavirin in patients with ESRD, therefore, carries a significant risk of hemolytic anemia. A recent randomized trial compared PegIFN monotherapy *vs* the combination of PegIFN and ribavirin 200 mg daily in treatment naïve HCV genotype 1 hemodialysis patients[121]. The combination therapy group had a significantly lower hemoglobin level (less than 8.5 g/dL) compared to monotherapy group (72% *vs* 6%, $P < 0.001$) but a significantly higher SVR rate (64% *vs* 33%, $P < 0.001$). The drop out rate was slightly higher in combination therapy group compared to monotherapy group (7% *vs* 4%). A systemic review revealed that combination therapy of PegIFN plus ribavirin in hemodialysis patients with HCV infection resulted in SVR rate of 56% and dropout rate of 25%[122]. Heart failure and anemia were recognized as the main reasons for the high dropout rate[102]. Patients for combination therapy with IFN and ribavirin are recommended to receive a lower dose of Ribavirin of 200-400 mg three times weekly with closer monitoring for anemia at weekly intervals. Other strategies to prevent worsening of anemia is to optimize the use of erythropoietin and intravenous iron supplement[9].

The role of triple therapy consisting of first generation PI with the backbone of PegIFN and ribavirin in long-term hemodialysis HCV-genotype 1 patients remains unclear. A pilot study on the use of telaprevir-based triple therapy reported efficacy with good tolerability in ESRD patients who previously failed to achieve SVR with PegIFN/ribavirin therapy. Three out of 4 patients achieved undetectable HCV RNA at 12 wk with telaprevir-based triple therapy[123]. In another study, therapy with telaprevir, PegIFN plus ribavirin was evaluated in 7 HCV-infected ESRD patients on hemodialysis; six out of 7 patients achieved SVR with the majority (5/7 patients) developing

anemia < 10 g/dL[124]. Newer direct-acting antiviral agents are in the horizon, however as most studies or clinical trials did not include patients with abnormal renal function, the use of these newer anti-HCV treatments in patients with renal impairment requires further evaluation.

TREATMENT FOR CHRONIC HEPATITIS C IN POST-KIDNEY TRANSPLANT PATIENTS

In organ transplant setting, hepatitis C viral replications have been shown to increase significantly with chronic immunosuppression use and after corticosteroids treatment for acute rejection[125,126]. Treatment of HCV with IFN alpha after renal transplant showed variable graft rejections rates of 15%-100% and a 20% chance for permanent renal allograft failure[127]. A recent meta-analysis in HCV infected renal transplant patients who received anti-HCV therapy with conventional IFN or PegIFN with or without ribavirin found that the SVR rate was 26.6 % (95%CI: 15.0%-38.1%), dropout rate of 21.1% (95%CI: 10.9%-31.2%) and the graft rejection rate was 4% (95%CI: 0.8%-7.1%). In the PegIFN-based therapy the SVR was up to 40.6% and graft rejection rate was 4% while in conventional IFN-based therapy group, the SVR was only 20.9%, and graft dysfunction was 19.2%. Combination therapy of conventional IFN or PegIFN with ribavirin led to a better SVR rate compared to monotherapy, with the best results achieved with PegIFN and ribavirin combination[128]. In another study, it was shown that the risk of renal allograft rejection is higher in the first year post transplantation therefore delaying interferon treatment after the first anniversary of transplant is preferred[129]. However most guidelines do not recommend IFN treatment for HCV in kidney transplant recipients[9,26,55]. Initiating IFN therapy with the possibility of renal graft loss and return to the need for hemodialysis is probably justifiable and unavoidable in cases of severe rapidly progressive liver failure from fibrosing cholestatic hepatitis and life-threatening vasculitis[9]. Comprehensive discussion on the risks and benefits of such therapy must be made with the individual patient. As IFN treatment has a limited role in patients post renal transplant, studies on the use of IFN-free therapy in this group of patients is urgently required. The newer generation DAAs like sofosbuvir and daclatasvir have been reported to salvage liver transplant patients with HCV related fibrosing cholestasis[130].

There are limited data on the use of the new DAAs together with the calcineurin inhibitors like cyclosporins and tacrolimus in HCV-infected post renal transplant recipients. Prescribing information from boceprevir and telaprevir showed significant increase in plasma concentration of cyclosporin, sirolimus or tacrolimus, thus the plasma concentration level of these drugs should be monitored closely[77,131]. The AASLD/IDSA guideline does not recommend the co-administration of simeprevir and cyclosporine[132] based on a pharmacokinetic study of simeprevir, daclatasvir and ribavirin in recurrent hepatitis C patients after orthotopic liver transplant, where the simeprevir plasma concentration was found to be raised by 6-fold in the presence of cyclosporin[133]. According to the AASLD/IDSA guidelines, no dose adjustment is required for combination therapy of sofosbuvir and simeprevir when co-administered with tacrolimus based on studies in liver transplant patients.

CONCLUSION

HCV infection is strongly associated with CKD, as both the cause and the consequence. Furthermore, HCV imparts a major medical burden in renal patients and increases the mortality of ESRD patients whether maintained on hemodialysis or after renal transplant. Successful anti-HCV therapy in this setting ameliorates these poor outcomes. It is vital for clinicians involved in the care of HCV patients to recognize, diagnose and manage the kidney component of this viral infection. Annual testing for proteinuria and hematuria should be part of the screening tests in chronic hepatitis C patients. The management of HCV patients should also include prevention of modifiable risk factors for HCV related CKD like diabetes and hyperlipidemia. However without large-scale clinical trials in this subpopulation of HCV patients with associated kidney disease, the current recommendations and common day-to-day practice are based on extrapolation from the non-CKD population and incorporating necessary dose adjustments based on the pharmacology of these drugs. The poor tolerability and efficacy from current PegIFN and low dose ribavirin in HCV patients with ESRD, call for an urgent need for interferon-free anti-HCV regimens. Clinical studies on pharmacokinetics, safety and efficacy of the newer anti-HCV agents in this group of patients are ongoing[134]. With the rapid pace of development of the newer DAAs that we have been observing, interferon-free regimen may soon become a reality and will offer a new hope for everyone living with HCV.

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