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REVIEW

Management of patients with hepatitis C infection and renal disease

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Abstract

Hepatitis C virus (HCV) infection in patients with end-stage renal disease (ESRD) is associated with more rapid liver disease progression and reduced renal graft and patients' survival following kidney transplantation. Evaluations and management of HCV in patients with renal disease are challenging. The pharmacokinetics of interferons (IFN), ribavirin (RBV) and some direct acting antiviral (DAA), such as sofosbuvir, are altered in patients with ESRD. With dose adjustment and careful monitoring, treatment of HCV in patients with ESRD can be associated with sustained virological response (SVR) rates nearly comparable to that of patients with normal renal function. DAA-based regimens, especially the IFN-free and RBV-free regimens, are theoretically preferred for patients with ESRD and KT in order to increase SVR rates and to reduce treatment side effects. However, based on the data for pharmacokinetics, dosing safety and efficacy of DAA for patients with severe renal impairment are lacking. This review will be focused on the evaluations, available pharmacologic data, and management of HCV in patients with severe renal impairment, patients who underwent KT, and those who suffered from HCV-related renal disease, according to the available treatment options, including DAA.

Key words: Hepatitis C; Renal disease; Chronic kidney disease; Dialysis; Interferon; Direct acting antivirals; Cryoglobulinemia

Core tip: Hepatitis C virus (HCV) infection in patients with end-stage renal disease (ESRD) is associated with more rapid liver disease progression and reduced graft and patients' survival following kidney transplantation. The pharmacokinetics of interferons (IFN), ribavirin (RBV) and sofosbuvir are altered in patients with ESRD. With dose adjustment and careful monitoring, treatment of HCV can be safely utilized and successful in most patients with ESRD. direct acting antiviral (DAA)-based regimens, especially IFN-/RBV-free regimens, are preferred for patients with ESRD and kidney

transplantation (KT). However, due to inadequate data on clinical safety and efficacy, DAA-based therapies are not currently recommended in patients with severe renal disease. This review will be focused on evaluations and management of HCV in ESRD, KT recipients and HCV-related renal disease, according to the available treatment options including DAA.

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INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a leading cause of chronic liver disease and hepatocellular carcinoma worldwide which over is a worldwide health problem in that it has a global prevalence rate of approximately 3% and affects over 170 million individuals[1]. In clinical practice, it is common to see HCV patients with pre-existing renal disease. Thus, the prevalence of HCV infection is apparently increased in patients with end-stage renal disease (ESRD) on chronic replacement therapy, especially hemodialysis. Importantly, the liver-related morbidity and mortality of HCV appear to be higher in patients with ESRD than in the general population[2-4]. For patients undergoing kidney transplantation (KT), HCV infection is associated with an increased rate of liver fibrosis, and the possibility of negatively affecting the renal graft and patients' survival[2-4].

Management of HCV in patients with renal disease presents unique challenges. The pharmacokinetics of interferons (IFN) and ribavirin (RBV) are altered in patients with renal disease, particularly with ESRD[2-4]. With dose adjustment and careful monitoring, treatment with pegylated interferons (PEG-IFN) with or without RBV can eradicate HCV infection in 40%-50% of ESRD patients infected with genotype 1/4 and about 80% of ERSD patients infected with genotype 2 or 3, with an incidence of discontinuation of up to 33%[2-4]. All HCV-positive KT candidates should be assessed to receive antiviral treatment prior to transplantation due to the increased risk of progression of liver disease with immunosuppressive therapy and the inability to receive IFN therapy after KT. Theoretically, the use of direct acting antiviral (DAA)-based regimens, especially the IFN-free and RBV-free regimens, is preferred for patients with ESRD and KT in order to increase sustained virological response (SVR) rates and to reduce treatment side effects. However, the data on pharmacokinetics, dosing safety and efficacy of DAA for patients with severe renal impairment are lacking. In addition, the availability of DAA is currently limited in many countries, especially in the developing world, mainly due to socio-economic reasons. Therefore, this review will be focused on the evaluation and management of HCV in patients with severe renal impairment, patients who underwent KT, and those who suffered from HCV-related renal disease, according to the available treatment options.

NATURAL HISTORY OF HCV IN PATIENTS WITH RENAL DISEASE

End-stage renal disease

The natural history of HCV in patients with ESRD is relatively uncertain[3]. Nevertheless, several studies have demonstrated that ESRD on dialysis is associated with an increased risk for all-cause and liver-related mortality[3,5,6]. Cardiovascular disease remains, however, the major cause of death in dialysis patients irrespective of HCV status[1]. Death from cirrhosis and hepatocellular carcinoma was notably higher among HCV-positive ESRD patients[5]. A meta-analysis on survival in dialysis patients (7 studies; n = 11589) showed an estimated relative risk for death in anti-HCV positive patients of 1.34 (95%CI: 1.13-1.59) with liver-related complications contributing to poorer outcomes[5]. Moreover, HCV infection can adversely affect the quality of life in this population[7].

KT

The impact of immunosuppression on HCV disease progression following renal transplantation is unclear. Serum HCV-RNA levels typically increase. Most data suggested that HCV-infected patients have worsening of hepatic necroinflammation and accelerated hepatic fibrosis following KT[8-10], though some studies reported that liver histology may remain stable or even improve[11,12]. Not only affecting the liver, several studies demonstrated that patients with HCV infection have a poorer patient and graft survival after KT compared to those without[3,13,14]. The exact reason for reduced renal graft survival in HCV patients is unknown, but it may partly explain by de novo immune complex chronic glomerulonephritis in the allograft induced by chronic HCV infection[15,16]. Nevertheless, undergoing KT evidently conferred a long-term survival advantages, particularly on the cardiovascular death, over HCV patients with ESRD on maintenance dialysis on the waitlist, although there was a higher risk for infection-related death during the first 6 mo after KT[11]. As cirrhosis is an key predictor of poor survival after KT, assessment of the stage of liver fibrosis in all HCV-positive KT candidates is recommended[17]. For patients with established cirrhosis and portal hypertension who failed (or are not suitable for) HCV treatment, isolated KT may be inappropriate in this settings and a combined liver and KT should be considered[18].

HCV infection acquired during or after RT showed a severe and rapidly progressive course, which is significantly different from HCV patients without transplantation[19]. In addition, fibrosing cholestatic hepatitis (FCH) can occur in HCV-infected patients following KT[20]. It typically develops during the period of maximal immunosuppression (1-4 mo after KT) and is associated with progressive cholestatic, mild elevation of serum alanine aminotransferase (ALT), and high HCV viremia level[20-22]. FCH is associated with very high morbidity and mortality rates. IFN-based treatment is often ineffective and is associated with a risk of graft rejection[20-22].

EVALUATIONS OF HCV IN PATIENTS WITH RENAL DISEASE

Serum aminotransferases

It is known that serum ALT levels in patients with ESRD are lower than in the general population, so it should not be used to screen for liver diseases[23-25]. This is possibly due to suppression of ALT synthesis in hepatocytes, defective release of ALT into the blood stream, or accelerated clearance in patients with chronic renal insufficiency[24,26]. The lower cut-off ALT level (⩾ 27 U/L) was proposed for patients with ESRD to increase sensitivity (to 50%) and specificity (to 100%) for detecting HCV viremia[23]. In addition, there is a weak correlation between ALT levels and liver disease activity in patients with ESRD, especially those on dialysis[25].

Viral markers

Anti-HCV assay by enzyme immunoassay (EIA) technique is the most commonly used screening tool for HCV infection due to its simplicity, availability and low cost. The second generation EIA (EIA-2) assay was frequently associated with false negative results in patients with ESRD on dialysis, with a reported rate of 2.6%-7%[27,28]. The third generation EIA (EIA-3) testing provided excellent accuracy, with 0.26% false-negative rate, and is the preferred screening tool in this setting[3,25,29]. PCR-based molecular diagnostics are required to confirm viremia, viral load, and genotype to guide management decisions. Notably, HCV-RNA level is transiently decreased during hemodialysis and gradually returns to baseline level within 48 h[3]. This may be explained by several mechanisms, such as interference with PCR technique by heparin used during dialysis, adsorption of HCV onto the dialysis membrane, destruction of HCV particles by the hydraulic pressure, escape of HCV into the dialysate, or increased plasma IFN levels during the dialysis[3,25]. Therefore, it is recommended to determine HCV-RNA level before hemodialysis to avoid the possibility of underestimation[3].

Assessment for liver fibrosis

Liver biopsy is the gold standard for assessing the degree of fibrosis in HCV patients. However, its use is limited by invasive nature, poor patient acceptance, and bleeding risk, especially in uremic patients. The use of non-invasive fibrotic markers has been evaluated in HCV patients with ESRD. The aspartate transaminase: platelet ratio index (APRI) can reliably predict liver fibrosis in HCV patients with ESRD, especially to exclude patients with significant fibrosis[30-32]. In Schiavon *et al*[31] study (203 ESRD HCV-infected subjects), APRI < 0.40 accurately identified patients with fibrosis stage 0 or 1 with negative predictive value of 93%; APRI ⩾ 0.95 can confirm significant fibrosis (⩾ fibrosis stage 2) with positive predictive value of 66%[31]. If biopsy indication was restricted to APRI scores in the intermediate range, about 50% of liver biopsies could be avoided[31]. Transient elastography shows superior diagnostic accuracy to APRI in HCV patients with ESRD[3,32]. The suggested optimized cut-off values were 5.3 kPa, 8.3 kPa, and 9.2 kPa, for fibrosis stage of ⩾ F2, ⩾ F3, and F4, respectively (sensitivity 93%-100% and specificity 88%-99%)[32]. Further, a small study (n = 22) revealed a good correlation between transient elastography and fibrosis stage on histology in HCV-positive KT recipients[33].

EPIDEMIOLOGY AND SCREENING OF HCV IN PATIENTS WITH ESRD ON DIALYSIS

The prevalence of HCV infection in patients with ESRD patients varies among geographical areas and dialysis centers, but it is obviously higher than that of the general population[2]. Risk factors for acquiring HCV infection during dialysis include: the number of transfusions, duration of dialysis, number of procedures for dialysis access, type of dialysis; hemodialysis (HD) > peritoneal dialysis (PD), prevalence of HCV infection and lack of compliance with universal precautions in the dialysis unit[34,35].

In developed countries, the prevalence and incidence of HCV has been declining in the past decades[2,36-38]. In the United States national surveillance (n = 164845), the prevalence of anti-HCV positivity has dropped from 10.4% in 1985 to 7.8% in 2002 (ranged from 5.5%-9.8%)[37]. Similarly, the European multicenter survey reported that the prevalence of anti-HCV positivity has dropped steadily from 13.5% in 1991 to 6.8% in 2000 in the Belgian cohort (n = 1710); prevalence also decreased (P < 0.05) in France (42% to 30%), Sweden (16% to 9%) and Italy (28% to 16%), tended to decrease in United Kingdom (7% to 3%, P = 0.058) and Hungary (26% to 15%, P = 0.057), but

did not change (NS) in Germany (7% to 6%), Spain (5% to 12%) and Poland (42% to 44%)[36]. Despite the elimination of post transfusion HCV infection, the incidence of HCV infection among patients on chronic dialysis treatment, with seroconversion rates ranging between 0.2%-15% per year of dialysis, continues to be a cause of concern[2,36-38]. The data on epidemiology of HCV among patients with ESRD on dialysis in developing countries are less abundant and more heterogeneous, but the overall prevalence and incidence rates seem to be higher than developed countries[2]. The prevalence of anti-HCV positivity in single center surveys from Brazil (2005), Turkey (2005), Tunisia (2006), Iran (2005), Saudi Arabia (2004), Morocco (2005) and Egypt (2000) were 8%, 19%, 20%, 25%, 43%, 76%, and 80%, respectively[2]. Whereas in the Asia-Pacific dialysis registry (173788 HD; 27802 PD), HCV seroprevalences range between 0.7%-18.1% across different countries and were generally higher in HD *vs* PD populations (7.9% ± 5.5% *vs* 3.0% ± 2.0%, $P = 0.01$)[38]. Thus, the annual incidence of HCV infections range from 0% in Thai PD patients to 18.1% in Indian HD patients with the rates were generally higher in HD patients than in PD patients (RR 0.33, 95%CI: 0.13-0.75)[38].

Although prospective trials have shown a reduction in HCV transmission within dialysis units by complete isolation of HCV patients, but this practice has not been universally accepted[2,39]. The Centers for Disease Control and Prevention of the US (CDC) and the Kidney Disease: Improving Global Outcomes (KDIGO) practice guidelines[40] do not recommend dedicated machines, patients isolation, or a ban on reuse in HCV patients on hemodialysis[40,41]. However, strict adherence to "universal precautions", careful attention to hygiene, and sterilization of dialysis machines is emphasized[40,41]. Further, the CDC recommends that all HD patients should be screened for anti-HCV at baseline, and then subsequently tested semiannually[41].

PHARMACOLOGIC ISSUES OF ANTIVIRAL AGENTS IN PATIENTS WITH RENAL DISEASE

Interferons and pegylated interferons

Interferon-alfa is a glycoprotein, produced by immune cells in response to foreign antigens, such as viruses, bacteria, parasites or tumor cells. The elimination half-life of IFN following subcutaneous injections is approximately 2-4 h, then it is filtered through the glomeruli and during proximal tubular reabsorption undergo lysosomal proteolytic degradation[25,42]. Kidney is the main site of degradation of IFN molecule, while liver plays only a minor role. Due to a short elimination half-life of IFN following subcutaneous injections (2-4 h), sustained plasma levels are not maintained when dosed 3 times weekly, which is believed in part to explain the suboptimal response rates[25,42]. Accumulation of IFN occurs in patients with renal dysfunction, especially in ESRD[25,42,43]. Although this may result in higher and more sustained plasma levels of IFN, which is preferable for the anti-viral activity against HCV, it may lead to serious adverse events in such patients as well[25,42,43].

Combing a polyethylene glycol (PEG) polymer to IFN successfully created a molecule with a longer half-life, improved pharmacokinetic profile, and more importantly, a superior clinical response when dosed once weekly[44,45]. PEG-IFN alfa-2a, a branched-PEG (40 kD) attached to an IFN alfa-2a molecule, is absorbed slowly (absorption half-life approximately 50 h), has a restricted volume of distribution (2-12 L), and a long elimination half-life (half-life approximately 77 h; peak through ratio 1.5-2)[44,45]. PEG-IFN alfa-2b, a linear PEG molecule (12 kD) attached to IFN alfa-2b, is absorbed rapidly (absorption half-life approximately 4.6 h), has a large volume of distribution (0.9 L/kg) and a shorter elimination half-life (half-life approximately 40 h; peak through ratio > 10)[44,45]. PEG-IFN alfa-2a is metabolized in the liver and kidneys while PEG-IFN alfa-2b is metabolized exclusively by the kidneys[25,44,45]. The pharmacokinetics of PEG-IFN alfa-2a is less affected by renal failure, and less dose modifications are necessary in the setting of renal impairment as compared to PEG-IFN alfa-2b (Table 1)[44,45]. In patients with severe renal impairment [creatinine clearance (CrCl) < 30 mL/min], the maximum plasma concentration and the area under the curve (AUC) of PEG-IFN alfa-2b are increased by approximately 90% and half-life is increased by approximately 40%[46]. Similar pharmacokinetic profiles have been also observed for PEG-IFN alfa-2a[25,45,46]. In addition, hemodialysis has only a small effect on IFN and PEG-IFN clearance[25,45,46].

Ribavirin

After oral absorption, RBV is rapidly absorbed and distributed with a bioavailability of approximately 50%. It has extensive volume of distribution and the steady state is reached in 7-11 wk after multiple dosing and with a terminal half-life of 12 d[47-49]. The route of RBV elimination is mainly by the kidney. Thus, body weight is also highly correlated with RBV clearance[47-49]. Notably, the optimal dosing strategy of RBV must be calculated according to the renal function, as measured by CrCl[47-49]. The AUC for RBV is increased by 2 folds in patients with CrCl 30-60 mL/min and by 3 folds in patients with CrCl 10-30 mL/min respectively, when compared to those with CrCl > 90 mL/min[50]. Notably, the most pronounced side effect of RBV in patients with renal disease is hemolytic anemia. The mechanism of RBV-induced anemia is unclear, but evidently involves an extensive accumulation of active RBV metabolites

Table 1 Dosage modification for patients with renal impairment

Creatinine clearance	Pegylated-interferon alfa-2a	Pegylated-interferon alfa-2b	Ribavirin
30-50 mL/min	180 μg/wk	1.125 μg/kg per week (25% reduction)	Alternating doses; 200 mg and 400 mg every other day
< 30 mL/min	135 μg/wk (25%-45% reduction)	0.75 μg/kg per week (50% reduction)	200 mg/d
Hemodialysis	135 μg/wk (25%-45% reduction)	0.75 μg/kg per week (50% reduction)	200 mg/d

Table 2 Pharmacokinetic and metabolic parameters of selected direct acting antivirals

Drugs	Metabolism/excretion route	Interaction with CYP3A	Comments
NS3/4A protease inhibitors			
Boceprevir	Hepatic (CYP3A, aldoketoreductase)	Moderate CYP3A inhibitor	Significant DDI with other CYP3A substrate drugs
Telaprevir	Hepatic (CYP3A)	Strong CYP3A inhibitor	Significant DDI with other CYP3A and P-gp substrate drugs
Simeprevir	Hepatic (CYP3A)	Mild CYP1A2 and CYP3A inhibitor	Unconjugated hyperbilirubinemia commonly seen
Faldaprevir	Hepatic (CYP3A)	Moderate CYP3A inhibitor; weak CYP2C9 inhibitor	Inhibition of UGTA1 results in unconjugated hyperbilirubinemia
ABT-450/ ritonavir	Hepatic (CYP3A)	Strong CYP3A inhibitor (by ritonavir)	Unconjugated hyperbilirubinemia
NS5A replication complex inhibitors			
Daclatasvir	Hepatic (CYP3A)	No/minimal	
Ledipasvir	Feces (major); hepatic and renal (minor)	No/minimal	
NS5B nucleos(t)ide polymerase inhibitors			
Sofosbuvir	Renal	No/minimal	Dose reduction if moderate to severe renal impairment
NS5B non-nucleoside polymerase inhibitors			
ABT-333	Hepatic (CYP2C8 60%, CYP3A4 30% and CYP2D6 10%)	No/minimal	

Adapted from Tischer *et al*[55]. CYP3A4: Cytochrome P450 3A4.

and subsequent oxidative stress within red blood cells (RBC)[51]. Ribavirin is actively transported into RBC and accumulates within RBC with the concentration greatly exceeding what is observed in plasma (up to 60-fold)[47,51,52]. Once inside RBC, RBV is phosphorylated to RBV-triphosphate, then it is eliminated slowly from RBC[47,51,52]. An increase in RBV-triphosphate concentrations in RBC enhances oxidative stress with subsequent RBC membrane damage, leading to premature extravascular destruction of RBC by reticuloendothelial system[51,52].

With careful monitoring, reduced dose PEG-IFN plus markedly reduced dose RBV (170-400 mg/d) has been safety utilized in patients with renal impairment, as well as those patients on dialysis[47,49]. However, the use of RBV in HCV patients on dialysis has not been well studied and it should be used with extreme caution and close follow. Further, minimal amount of RBV is removed by dialysis so that there is a potential risk of drug accumulation[25]. Despite this, there are some data to support the use of RBV in dialysis patients by starting empirically with a low dose of 200 mg/d, then adjusting doses according to changes in hemoglobin[47,49,53]. Notably, erythropoiesis-stimulating agents may be used to counteract anemia and help maintain optimal RBV dose in patients with renal disease[47,49]. Until recently, the use of RBV in persons with CrCl < 50 mL/min was contraindicated due to a markedly reduced ribavirin elimination rate, leading to severe hemolytic anemia. However, the US Food and Drug Administration (US-FDA) has approved a labeling change of RBV for patients with severe renal impairment with recommended dosage modifications since 2011[54] (Table 1). It should be noted that breaking RBV tablet into half is not advised due to the potential environmental contamination of this serious teratogen. Given its extensive Vd and long half-life, RBV can be finely adjusted by alternating daily dosage[47,49].

Direct acting antivirals

Most Direct acting antiviral (DAA) are metabolized primarily *via* the liver and dose adjustment is not necessary for patients with renal impairment[55,56] (Table 2). However, it should be noted that these agents have not been adequately evaluated for the treatment of HCV in patients with renal impairment in clinical trials in terms of safety and efficacy. *In vitro* studies indicate that boceprevir (BOC) extensively

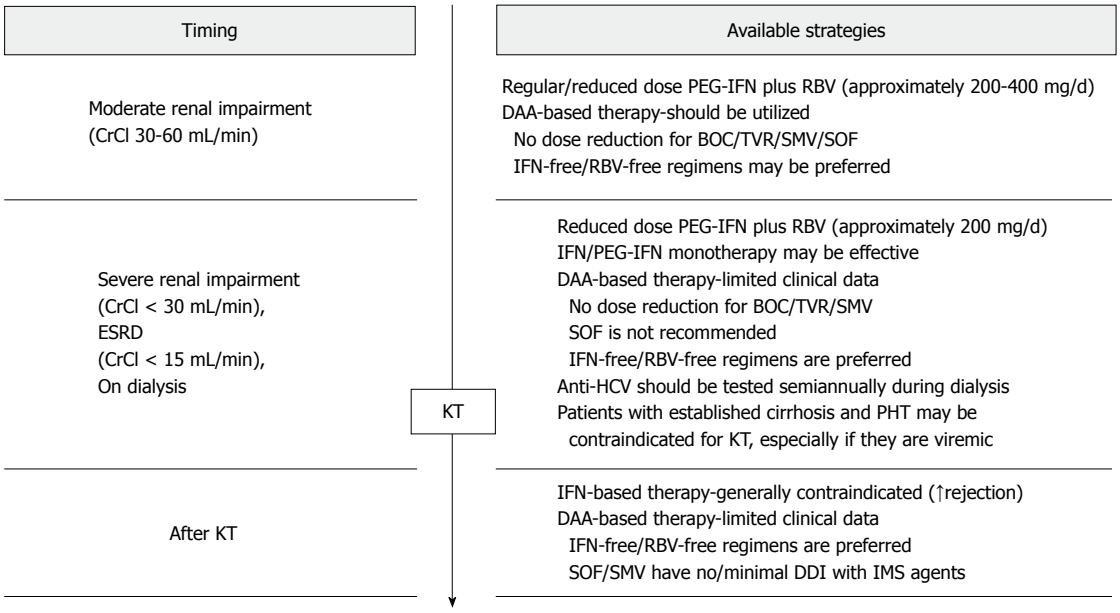

Figure 1 Management of hepatitis C virus in patients with renal disease and kidney transplantation. Empiric dose changes should be done in conjunction with therapeutic drug monitoring. BOC: Boceprevir; TVR: Telaprevir; SMV: Simeprevir; SFV: Sofosbuvir; CYP3A4: Cytochrome P450 3A4; mTOR: Mammalian target of rapamycin; MMF: Mycophenolate mofetil.

undergoes metabolism through the aldo-keto reductase-mediated pathway and, to a lesser extent, oxidative metabolism mediated by CYP3A4 in the liver[54]. Telaprevir (TVR) is primarily metabolized in the liver involving hydrolysis, oxidation, and reduction[54]. No dose adjustment is required for BOC and TVR in patients with any degree of renal impairment[54]. Simeprevir (SMV) is metabolized by liver CYP3A4 and kidney clearance plays an insignificant role (< 1%)[57]. A pharmacokinetic study in volunteers demonstrated that SMV exposure after 7 d of 150 mg/d dosing was 62% higher in patients with severe renal impairment compared with matched healthy volunteers, but safety and tolerability were considered generally favorable[57]. Daclastavir is also metabolized primarily by the liver, and the need for dose adjustment in patients with impaired renal function is unknown[55,56]. Unlike the others, sofosbuvir (SOF) is excreted *via* the kidneys. A single 400-mg dose of SOF resulted in 56%, 90%, and 456% higher levels of the major systemic metabolite, GS-331007, among persons with mild, moderate, and severe renal dysfunction, respectively, compared with individuals with normal renal function[58].

MANAGEMENT OF HCV IN PATIENTS WITH ESRD

Interferon or pegylated interferon monotherapy

There have been at least 4 meta-analyses demonstrating that IFN monotherapy is effective for HCV patients with ESRD, with the overall SVR rates of 33%-41% and the withdrawal rates of 17%-30%[59-62]. The discontinuation of treatment were mainly due to flu-like symptoms, gastrointestinal and hematological adverse events, which is more frequent than in patients with normal renal function[59-62]. Notably, the use of PEG-IFN does not seem to provide an additional benefit in terms of SVR compared to conventional IFN monotherapy in patients on dialysis[61,62]. This finding may largely explain by changes in the pharmacokinetics of IFN toward increasing half-life and AUC (more similar to that of PEG-IFN) in the setting of ESRD. In a recent meta-analysis of 25 studies (included 459 patients treated with IFN38 patients treated with PEG-IFNand 49 patients treated with PEG-IFN/RBV), the overall SVR rate was 41% (95%CI: 33-49) for IFN and 37% (95%CI: 9-77) for PEG-IFN[61]. Treatment discontinuation rates were 26% (95%CI: 20%-34%) for IFN and 28% (95%CI: 12%-53%) for PEG-IFN. The SVR rate tended to be higher when 3 million units or higher of IFN 3 times weekly were used[61] (Figure 1).

Interferon or pegylated interferon plus ribavirin

In patients with normal renal function, the addition of RBV to IFN or PEG-IFN is generally required in order to achieve an optimal SVR, primarily by decreasing relapse rates[47]. Several small studies have demonstrated that the use low-dose RBV (from 200 mg/wk to 400 mg/d) in combination with IFN-based therapy was feasible for treating HCV patients with ESRD[3,50]. Despite the widespread use of high-dose erythropoietin, falling hemoglobin levels were commonly observed[3,50]. Overall, SVR and treatment-related withdrawal rates after 24-48 wk of combination therapy ranged between 17%-90% and 0%-70%, respectively[3,50]. Rendina *et al*[63] reported a case series evaluating PEG-IFN 135 μg/

wk plus RBV 200 mg/d for 24 (non-G1) or 48 wk (G1) in HCV patients on dialysis[63]. In this study, 35 patients received treatment (35 served as untreated controls), and 30 patients completed treatment (drop-out rate 14%)[63]. Overall, 34 of 35 (97%) treated patients, including those with treatment discontinuation due to side effects, achieved SVR[63]. Recently, an open-label, randomized trial in Taiwan randomized 205 HCV patients on hemodialysis to PEG-IFN 135 μg/wk plus RBV 200 mg/d (n = 103) or PEG-IFN 135 μg/wk alone (n = 102) for 48 wk[53]. Compared with monotherapy, combination therapy had a greater SVR rate (64% *vs* 33%, $P < 0.001$)[53]. More patients receiving combination therapy required a higher dosage and longer duration of epoetin-beta and had more hemoglobin levels < 8.5 g/dL than those receiving monotherapy (72% *vs* 6%, $P < 0.001$)[53]. The adverse event-related withdrawal rates were similar between the two groups[53]. The recent AASLD/IDSA guidance recommended patients with renal impairment/ESRD/HD, dosing of PEG-IFN and RBV to follow updated FDA recommendations or package insert recommendations based on calculated glomerular filtration rate[64].

Boceprevir- or telaprevir-based triple therapy

The first wave DAA, boceprevir (BOC) and telaprevir (TVR), in combination with PEG-IFN/RBV has been the standard of care of HCV genotype 1 in many countries since 2011, with an improvement in SVR up to 65%-75% in treatment naïve patients and 60%-65% in previous relapsers/non-responders[1]. Notably, patients with CrCl < 50 mL/min or those with ESRD were excluded from their registration trials[1]. Despite the lack of required dose adjustment, there have been very few small case series evaluating the safety and efficacy of these protease inhibitors in patients with ESRD on dialysis[65-67]. Therefore, the routine use of BOC/TVR-based triple therapy routine use in patients with severe renal impairment cannot be recommended[54,64]. It is possible that treatment-related side effects, particularly anemia, will be increased in patients with renal disease. Thus, the potential drug-drug interactions between the BOC/TVR and concomitant medications that commonly used in patients with ESRD (*e.g.,* antihypertensive and lipid lowering agents) may further complicate the therapy.

Sofosbuvir- and simeprevir-based therapy

SOF and SMV have recently been approved for the treatment of HCV in United States and many countries in Europe. In settings where available, SOF- and SMV-containing regimens are preferred for over BOC/TVR-based triple therapy due to superior efficacy, more convenience dosing, and less drug-drug interactions[64]. Ideally, patients with ESRD should receive an IFN-free, and if possible RBV-free treatment regimen. Based on the available data, the recent AASLD/IDSA guidance advised that no dose reduction is needed when using SOF in patients with HCV infection with mild to moderate renal impairment (CrCl ⩾ 30 mL/min). However, SOF is not recommended in patients with severe renal impairment and ESRD (CrCl < 30 mL/min) or those who require HD until more data available[64]. For SMV, no dosage adjustment is required for patients with any degree of renal impairment. SMV has not been adequately studied in patients with ESRD, including those requiring HD[64].

MANAGEMENT OF HCV IN KIDNEY TRANSPLANT RECIPIENTS

Interferon- or pegylated interferon-based therapy

Outcomes of IFN-based treatment after KT are somewhat disappointing. In a meta-analysis of 12 clinical trials (102 RT recipients with HCV), treatment with IFN with or without RBV is associated with the overall SVR and treatment-related withdrawal rates of 18% and 35%, respectively[68]. More recent meta-analysis (n = 140) reported that the overall SVR rate, drop-out rate and graft rejection rate was 26.6%, 21.1% and 4%, respectively[69]. Thus, PEG-IFN may be a more effective approach for treating HCV post-KT than standard IFN-based treatment (SVR: 40.6% *vs* 20.9%)[69]. These suboptimal SVR rates may largely explain by the interruption of treatment by side effects and the limited efficacy of IFN in immunosuppressed patients. In addition, the immunostimulatory effects of IFN, including increased expression of cytokines and HLA antigens, and enhanced function of cytotoxic T cells and natural killer cells, can lead to an increased risk of acute allograft rejection in KT recipients[4]. The early studies reported that graft dysfunction occurred in 15%-100% of HCV-positive KT recipients treated with IFN, with up to 20% resultant permanent allograft failure[4,70-73]. Although more recent studies revealed that PEG-IFN/RBV treatment may be feasible for KT recipients and the development of graft rejection was in fact relatively rare (0%-5%), but the SVR rates are still relatively low (38%-50%)[74-76]. Taken together, IFN-based therapy should only be initiated in KT recipients under specific clinical situations, such as FCH or severe de novo glomerulonephritis, where DAA are unavailable and when the risk of not treating HCV infection outweighs the risk of graft loss (Figure 1).

Boceprevir- or telaprevir-based triple therapy

Both BOC and TVR are substrates for and inhibitors of the CYP3A4 and the drug transporter P-glycoprotein, so that they are prone to interact with other medications involving this enzyme[55,56,77]. Several studies have demonstrated that co-administration

of BOC and TVR significantly increased the dose exposure of cyclosporine, tacrolimus and mammalian target of rapamycin (mTOR) inhibitors by several folds[55,56,77]. Lessons from LT suggested that the drug-drug interaction issues with BOC- and TVR-based triple therapy may be manageable with preemptive dose reduction and close monitoring of immunosuppressive drug levels[55,56,77]. However, the use of BOC/TVR-based triple therapy may not be suitable for KT setting due to the possible rejection issue with IFN.

Sofosbuvir- and simeprevir-based therapy

KT recipients with an indication for HCV treatment should receive IFN-free regimen. SOF does not undergo metabolism *via* hepatic CYP3A, limiting the likelihood of drug-drug interactions with immunosuppressive agents that are inducers or inhibitors of this enzyme[55,56]. However, SOF is a substrate for P-gp and should not be coadministered with potent P-gp inducers such as rifampin or St John's wort. SMV is a mild CYP3A inhibitor and weak drug-drug interaction may be observed when co-administration with immunosuppressive agents. For example, the AUC of tacrolimus decreased by 17% and that of cyclosporine increased by 19% with SMV co-administration[78]. However, the package insert for SMV advises that no dose adjustments are needed during co-administration with cyclosporine or tacrolimus. Monitoring of sirolimus concentrations may be advisable when given with SMV.

HEPATITIS C VIRUS-RELATED RENAL DISEASE

Epidemiology

Considering HCV is both a hepatotrophic and lymphotrophic virus, in addition to causing a liver disease, it can be associated with a number of lymphoproliferative and immunological disorders of various organ systems, including the kidney[79] (Figure 2). HCV-related renal disease can affect both glomerular and tubular component, which can be presented with a wide array of clinical manifestations, ranging from asymptomatic proteinuria, overt glomerular disease, to ESRD. Notably, the most common and well-established renal involvement of HCV is mixed cryoglobulinemia (MC)-associated glomerulonephritis[16,79-81]. Whereas other conditions such as membranoproliferative glomerulonephritis (MPGN) and membranous nephropathy, focal segmental glomerulosclerosis, fibrillary glomerulonephritis, immunotactoid glomerulopathy, IgA nephropathy, mesangial proliferative glomerular nephritis, renal thrombotic microangiopathy, vasculitic renal involvement and interstitial nephritis are less commonly described[16,80]. These pathologic findings are not specific for HCV and the diagnosis of HCV-related renal disease has to be made cautiously with exclusion of the other secondary causes. In most circumstances, renal involvement itself does not affect overall survival in HCV infected patients but it could modify natural course of disease significantly[82].

The prevalence of HCV-related renal disease varies among reports and also seems to be geographical heterogeneity. For example, the prevalence of MC is clearly more prevalent in Southern Europe (more than 50% of HCV-infected individuals) than in Northern Europe, North America, and Asia[79,81]. One large epidemiologic study among US veterans showed that cryoglobulinemia and MPGN, not membranous glomerulopathy, are more prevalent in HCV-infected patients (n = 34204) compared to non-HCV controls (n = 136816): 0.57% *vs* 0.05%; $P < 0.001$, 0.36% *vs* 0.05%; $P < 0.001$ and 0.33% *vs* 0.19%; $P = 0.86$, respectively[83]. In addition, HCV infection is independently associated with proteinuria[84,85]. Besides, many epidemiological studies have shown an association between HCV and diabetes mellitus, especially type 2[86]. The processes seem to involve direct viral effects, insulin resistance, proinflammatory cytokines, chemokines, and other immune-mediated mechanisms[86]. Therefore, proteinuria and renal disease in such patients may be secondary from diabetic nephropathy, not directly related to HCV itself.

Diagnosis of mixed cryoglobulinemia

Cryoglobulinemia is a chronic systemic disease characterized by the presence of serum immunoglobulins that reversibly precipitate at low temperature[87]. Classically, cryoglobulemia is divided into 3 types. Type I composed of a monoclonal immunoglobulin associated mainly with overt lymphoproliferative disorders and is classically presented with vascular occlusion or hyperviscosity syndrome[80,88]. Type Ⅱ and Ⅲ, so-called MC, consisted of polyclonal IgG and monoclonal/polyclonal IgM with rheumatoid factor. These two types are associated with infectious, immunological and neoplastic disorders (also can be idiopathic), and often present with vasculitis syndrome, *e.g.*, peripheral neuropathy, skin ulcers as well as glomerulonephritis[80,88]. The strong association between HCV and MC type Ⅱ and Ⅲ has been supported by several epidemiological studies[16,79-81,87]. HCV appears to have an important etiologic role in MC, as the evidence of HCV infection can be found in 76%-95% of patients with MC[89,90]. On the other hand, low level of cryoglobulinemia is commonly found in unselected HCV patients with prevalence 19%-54%[91,92]. Most of these patients are asymptomatic and about 5%-20% have an overt clinical of MC[91,92].

Diagnosis of MC is based on clinicopathological and laboratory work-up including cryoglobulin testing, quantitative serum protein and globulins, complement levels, virologic markers, and urine analysis. The

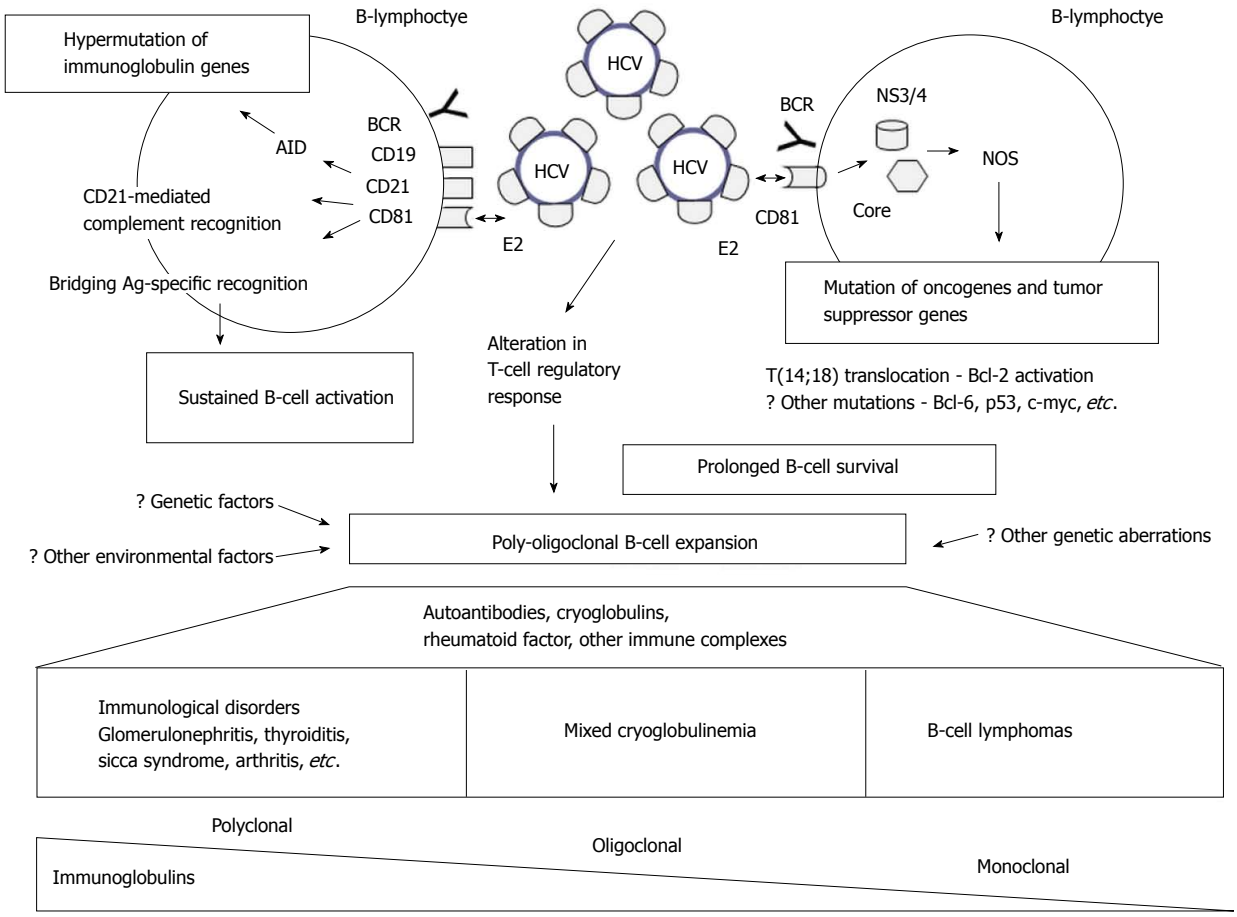

Figure 2 Proposed pathogenesis of hepatitis C virus-related immunogenic and lymphoproliferative disorders. HCV: Hepatitis C virus; NOS: Nitric oxide synthase; ROS: Reactive oxygen species; AID: Activation-induced deaminase.

clinical syndrome of MC caused by deposition of circulating immune complexes in small to medium-sized blood vessels in multiple organs, inducing systemic vasculitis. The main clinical manifestations of MC are palpable purpura, arthralgia, myalgia, peripheral neuropathy and hypocomplementemia[88,90]. Cryoglobulins can precipitate in vitro at temperatures of less than 37 ℃ (typically at 4 ℃[80]) and re-dissolve after rewarming[93].

Renal involvement is presented in up to one third of patients and represents a strong negative prognostic factor, even if their course may vary[90,94]. Nephropathy is observed in 20% at the diagnosis of MC, and in 35%-60% during follow up, in which the majority occurs within a few years[90,95]. Clinically, MC-associated glomerulonephritis may range from asymptomatic abnormal urinalysis (microscopic hematuria, or sub-nephrotic range proteinuria with normal, or mildly impaired, renal function), overt nephritis (20%-25%) and nephrotic syndrome (20%), with variable progression to end-stage renal disease in 10%-33% of patients[90,95]. The typical renal histopathologic pattern is type Ⅰ MPGN, which can be differentiated from idiopathic MPGN by the presence of capillary thrombi, composed of precipitated cryoglobulins, and diffuse IgM deposition in the capillary loops[80,90,96,97].

Treatment of mixed cryoglobulinemia-related glomerulonephritis

Several small studies reported a beneficial effect of PEG-IFN/RBV in patients with HCV-related MC with 62%-78% SVR rates[87,98]. PEG-IFN/RBV is generally well-tolerated (treatment-related side effects 22%-54%) in cryoglobulinemic patients and the dosage should be adjusted according to renal function[86,97]. Notably, the chance to achieve SVR is not affected by the presence of cryoglobulinemia[87,98]. Importantly, significant improvement of clinical MC syndrome and immunologic parameters is typically observed in patients who attained SVR. Cryoglobulin level often declines or even disappears after successful treatment. Though, MC-related vasculitis has been reported to persist or to relapse after achieving in a small proportion of patients[94,99]. A meta-analysis of controlled clinical trials suggested that IFN-based therapies were more effective than immunosuppressive agents in lowering proteinuria of patients with HCV-related cryoglobulinemic glomerulonephritis (OR = 3.86; 95%CI: 1.44-10.33)[100].

Recent studies in HCV-related MC with or without renal involvement demonstrated that triple therapy with TVR, BOC or SOF plus PEG-IFN/RBV are safe and effective in cryoglobulinemic patients[100-102]. However, such therapeutic regimens should be administered cautiously considering the high rate of side effects (up to 35% discontinuation rates)[101,103]. More clinical trials, especially with IFN-free regimens, are eagerly awaited.

Corticosteroids and cyclophosphamides have shown to effectively induce clinical remission in patients with severe MC. However, their effects are not sustainable and they can be associated with significant side effects, liver toxicity, and subsequent increase in HCV viremia[86,99]. Rituximab, a chimeric monoclonal antibody specifically directed against CD20 antigen, has been proven to be safe and effective in the treatment of MC with or without HCV[87,98,104]. A randomized controlled trial comparing between PEG-IFN/RBV with or without rituximab in treatment-naïve MC patients demonstrated that a combination of PEG-IFN/RBV plus rituximab is well tolerated and more effective than PEG-IFN/RBV alone[105]. Thus, its effect may last for more than 3 years[105]. Therefore, a combination of rituximab and antiviral therapy is recommended to treat in HCV-related MC with progressive kidney disease[40,87,106]. In addition, the removal of circulating cryoglobulins by therapeutic plasmapheresis combined with immunosuppressive agents, such as pulse corticosteroids, may be considered as an adjunctive therapy for severe exacerbation of vasculitis, especially rapidly progressive glomerulonephritis[40,87,106,107].

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