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TOPIC HIGHLIGHT

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Hepatitis C virus associated glomerulopathies

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Abstract

Hepatitis C virus (HCV) infection is a systemic disorder which is often associated with a number of extrahepatic manifestations including glomerulopathies. Patients with HCV infection were found to have a higher risk of end-stage renal disease. HCV positivity has also been linked to lower graft and patient survivals after kidney transplantation. Various histological types of renal diseases are reported in association with HCV infection including membranoproliferative glomerulonephritis (MPGN), membranous nephropathy, focal segmental glomerulosclerosis, fibrillary glomerulonephritis, immunotactoid glomerulopathy, IgA nephropathy, renal thrombotic microangiopathy, vasculitic renal involvement and interstitial nephritis. The most common type of HCV associated glomerulopathy is type Ⅰ MPGN associated with type Ⅱ mixed cryoglobulinemia. Clinically, typical renal manifestations in HCV-infected patients include proteinuria, microscopic hematuria, hypertension, acute nephritis and nephrotic syndrome. Three approaches may be suggested for the treatment of HCV-associated glomerulopathies and cryoglobulinemic renal disease: (1) antiviral therapy to prevent the further direct damage of HCV on kidneys and synthesis of immune-complexes; (2) B-cell depletion therapy to prevent formation of immune-complexes and cryoglobulins; and (3) nonspecific immunosuppressive therapy targeting inflammatory cells to prevent the synthesis of immune-complexes and to treat cryoglobulin associated vasculitis. In patients with moderate proteinuria and stable renal functions, anti-HCV therapy is advised to be started as pegylated interferon-α plus ribavirin. However in patients with nephrotic-range proteinuria and/or progressive kidney injury and other serious extra-renal manifestations, immunosuppressive therapy with cyclophosphamide, rituximab, steroid pulses and plasmapheresis should be administrated.

Key words: Hepatitis C virus infection; Glomerulopathy; Membranoproliferative glomerulonephritis; Cryoglobulinemia; Kidney transplantation; Membranous nephropathy; Diabetic nephropathy; IgA nephropathy; Focal segmental glomerulonephritis

Core tip: Hepatitis C virus (HCV) infection is found to be frequently associated with proteinuria, various glomerulopathies and higher risk of end-stage renal disease. HCV positivity has been linked to decreased graft and patient survivals after kidney transplantation. Treatment of HCV infection is a great clinical challenge in kidney transplant patients and in patients with diminished kidney function. In this review, we aimed to review kidney involvement in the course of HCV infection and treatment of HCV-associated glomerulopathies.

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INTRODUCTION

Incidence of hepatitis C virus (HCV) infection has been reported to be 3-4 million per year and it is known that 3% of the world's population is currently infected with HCV[1,2]. HCV infection should be considered as a systemic disorder which is often associated with a number of extrahepatic manifestations such as porphyria cutanea tarda, lichen planus, seronegative arthritis, type 2 diabetes mellitus, lymphoproliferative disorders, cryglobulinemia and glomerulopathies[3]. Almost 40% of patients with HCV develop at least one extrahepatic manifestation during the course of the disease[1]. HCV infection is known to be associated with proteinuria[4]. After kidney transplantation, HCV infection has been considered as a prognostic factor for the long-term renal allograft and patient survival[5]. Herein, we aimed to review kidney involvement in the course of HCV infection and treatment of HCV-associated glomerulopathies.

KIDNEY INVOLVEMENT IN THE COURSE OF HEPATITIS C VIRUS INFECTION

A significant relationship between HCV and proteinuria was suggested in otherwise healthy individuals[4,6-8]. The risk of proteinuria in patients with human immunodeficiency virus (HIV)-HCV co-infection was also found to be higher than in those with HIV infection alone[9]. Additionally, anti-HCV antibody positivity was observed to be significantly associated with proteinuria[4]. But no association could be found between HCV seropositivity and estimated glomerular filtration rate (eGFR)[6]. However, in a retrospective cohort study including more than 470000 adults, patients with HCV infection had higher risk of end-stage renal disease (ESRD) (4.3/1000 person-year) than patients without HCV infection (3.1/1000 person-year)[10]. Furthermore, in patients with an eGFR $\leqslant$ 30 mL/min per 1.73 m^2, HCV sero-positivity was related to a nearly threefold higher risk of ESRD. These findings were in parallel to the findings of a recent study concluding that patients with HCV-positivity had a 40% higher likelihood of renal insufficiency (serum creatinine levels $\geqslant$ 1.5 mg/dL) compared to seronegative patients[11]. With all these data in mind, it may be suggested that subclinical and under-diagnosed glomerulopathy is frequently present in the course of the HCV infection. Supporting this hypothesis, in a recent study, protocol renal biopsies were performed on patients with cirrhosis due to chronic HCV infection at the time of liver transplantation and immune complex-mediated glomerulonephritis was found in most of the patients (25 of 30 patients)[12].

Various histological types of renal diseases are reported in association with HCV infection including membranoproliferative glomerulonephritis (MPGN), membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), proliferative glomerulonephritis, fibrillary glomerulonephritis, immunotactoid glomerulopathy, IgA nephropathy, renal thrombotic microangiopathy, vasculitic renal involvement and interstitial nephritis[13-15]. Type I MPGN associated with type Ⅱ mixed cryoglobulinemia (MC) is the most common HCV-associated glomerulopathy.

The typical renal manifestations in HCV-infected patients include proteinuria, microscopic hematuria, hypertension, acute nephritis and nephrotic syndrome. However, mostly the renal disease is asymptomatic, and thus patients with HCV infection should be screened for proteinuria, hematuria, hypertension and cryoglobulinemia[12,16].

PATHOGENESIS OF HCV-RELATED KIDNEY DISEASES

HCV is able to bind and penetrate into the renal parenchymal cells *via* the CD81 and SR-B1 receptors[17]. HCV RNA has been found in mesangial cells, tubular epithelial cells, and endothelial cells of glomerular and tubular capillaries[18,19]. HCV-related granular protein deposits located in the mesangium were found to be related to higher degrees of proteinuria[19].

Mixed cryoglobulins are serum proteins reversibly precipitating in 4 ℃. Two types of MC are present - type Ⅱ and Ⅲ. Polyclonal immunoglobulin G (IgG) is bound to another immunoglobulin, which is an antiglobulin and acts as an anti-IgG rheumatoid factor (RF). In type Ⅱ MC, the antiglobulin is monoclonal, whereas in type Ⅲ MC, it is polyclonal. MC may be associated with infections, systemic autoimmune diseases, lymphoproliferative disorders and HCV infection[20,21]. HCV is known to be the cause of 80%-90% of MC. In general, HCV is associated with type Ⅱ MC, however it has also been reported to be associated with type Ⅲ MC[22,23]. The pathophysiological mechanism of HCV-related MC probably involves E2-CD81 interaction. The E2 protein of HCV interacts with CD81, the cellular receptor for HCV that is required for infection of hepatocytes. CD81 is also expressed on B lymphocytes and the E2-CD81 interaction leads to monoclonal proliferation of B lymphocytes and eventually HCV-related MC[24].

Cryoglobulins are deposited in the glomerular capillaries and mesangium and they appear as intense subendothelial IgM deposits by immunofluorescence microscopy. Cryoglobulins are also usually associated with histologic signs of vasculitis and downstream fibrinoid necrosis[17]. Cryoglobulin associated nephrotoxicity is suggested to be due to affinity of the IgM-RF for cellular fibronectin in the mesangial matrix[25,26]. Cryoglobulins may also induce endothelitis *via* anti-endothelial activity and complement activation leading to increased expression of VCAM-1 and platelet aggregation[17]. Actually cryoglobulinemic vasculitis is a systemic vasculitis that involves mostly small-sized arteries and veins in which immune complexes composed of RF, IgG, HCV RNA and complements are deposited on endothelial surfaces. Unlike the pattern seen in cutaneous vasculitis, HCV RNA is not the predominant component in immune complexes of kidney lesions[27].

Toll-like receptors (TLR) may also have a role in HCV-associated renal injury[28]. TLR3 expression was found to be increased in the mesangial cells of patients with HCV-related MPGN[29]. TLR4 is constitutively expressed by podocytes. Glomerular expressions of TLR4 and fibronectin were found to be upregulated in a murine model of cryoglobulinemic glomerulonephritis[30].

DIAGNOSIS OF HCV-INDUCED GLOMERULAR LESIONS

HCV-positive patients should be screened annually for microalbuminuria, microscopic hematuria, RF, cryoglobulinemia, complement factors and hypertension. If cryoglobulinemia is suspected, serum should be kept warm and tests should be carried out at 37 ℃. A kidney biopsy is required for patients with proteinuria, impaired renal function and cryoglobulinemia. Vice versa, patients with MPGN or MGN should be screened for HCV infection. HCV serology with a third-generation enzyme-linked immunosorbent assay and investigation of HCV RNA in the serum should be performed for this purpose[31].

In renal biopsies, electron microscopic detection of viral like particles has been reported in a few studies performed on HCV-infected patients[32,33]. However the diagnostic value of the electron microscope is questionable. In the study by Sabry *et al*[33], viral like particles were found within the immune complexes. HCV-related virus-like particles were about 30-45 nm in diameter and located in electron-dense deposits in the paramesangial areas[33].

CRYOGLOBULINEMIC GLOMERULONEPHRITIS

Patients with HCV-induced MC usually have no symptoms or clinical manifestations[34]. Renal involvement is reported in at least one third of patients with type Ⅱ MC having a prevalence ranging from 20% to 56% in various series[35,36].

The triad of purpura, asthenia, and arthralgia is present in 30% of these cases[37]. Cryoglobulinemic vasculitis is seen in only 2%-3% of patients[38,39]. Patients with HCV-associated cryoglobulinemic glomerulonephritis experience nephrotic or acute nephritic syndrome with deterioration of renal function in 20% and 30% of patients, respectively[40]. Patients with HCV-associated cryoglobulinemic glomerulonephritis present with oliguric acute renal failure in 5% of cases[20]. Most of the patients (80%) have severe hypertension. The serum levels of C4 and C1q are usually very low. Alanine aminotransferase levels are increased in 70% of patients. The majority of such patients are RF-positive[41]. The extra-renal manifestations are usually accompanied by the recurrence of renal disease. Renal disease generally shows an indolent course, and ESRD requiring dialysis treatment is relatively uncommon (10% of cases)[42].

Renal biopsy shows a pattern of MPGN[35]. Inflammatory cells infiltrate the glomerular capillaries. Mesangial matrix expansion, intracapillary accumulation of eosinophilic material and monocyte infiltration with double contours of the basement membranes may be observed[20]. Moreover, one-third of these patients may have vasculitis of small renal arteries. Extracapillary crescents are rarely seen[43]. Immunofluorescence microscopy may reveal C3, IgM and IgG depositions on the capillary wall and mesangium. Intraluminal and subendothelial deposits may have a fibrillary pattern on electron microscopy probably representing cryoglobulin deposition[40].

MPGN

Type I MPGN is the glomerulonephritis most strongly associated with chronic HCV infection. It should be investigated in anti-HCV-positive patients with proteinuria, cryoglobulinemia and hypocomplementemia. MPGN is mostly associated with type 2 MC[35,44]. The prevalence of MPGN is higher in HCV patients with cryoglobulinemia. HCV RNA has been reported to be present in 80% of cases of cryoglobulinemia-related MPGN but only in 25% of MPGN cases without cryoglobulinemia[45].

MPGN lesions are characterized by endocapillary proliferation, monocytic infiltration, double contour in basement membranes, large eosinophilic and PAS-positive intraluminal deposits and vasculitis of small and medium sized renal arteries[46]. On electron microscopy, subendothelial deposits are usually present and may have tubular and crystalline patterns similar to that of cryoglobulins[47]. In an autopsy study performed on 188 patients with HCV infection, the prevalence of glomerular deposition of immune complexes was found to be 54% which was significantly higher than the prevalence of symptomatic glomerulonephritis[16]. In this study, MPGN was the most common type of glomerulonephritis with a prevalence of 11%.

MN

Several cases of MN have been described in HCV-infected patients[48,49]. The clinical presentation and the histological findings of HCV-associated MN are similar to idiopathic MN. Usually serum complement levels are normal and cryoglobulins and RF are absent in the serum. Yamabe *et al*[44] found that 8% of MN patients were anti-HCV-positive or HCV RNA-positive compared to less than 1% of patients with other types of glomerulonephritis, excluding MPGN. In a study performed on kidney transplant recipients with HCV infection, 3.6% of the patients developed MN after kidney transplantation[50]. HCV RNA was detectable in all of these patients. Cryoglobulinemia, hypocomplementemia or RF were absent. The clinical presentation and histological picture were similar to posttransplant idiopathic *de novo* MN. In fact, 18.2% of renal biopsies of HCV-positive patients revealed MN compared to that of 7.7% in HCV-negative

patients. Thus HCV infection may be suggested to be related to MN after kidney transplantation.

FSGS

There are several reports about the association between HCV and FSGS[51,52]. Shah *et al*[52] reported a patient with HCV-associated FSGS who presented with nephrotic syndrome and renal failure. Treatment with pegylated interferon-α (PEG-IFN-α) monotherapy resulted in sustained virological response (SVR) with a clinical remission of nephrotic syndrome and stabilization of renal function and patients continued to remain in remission even 5 years after treatment. Combination therapy with IFN-α and ribavirin was reported to cause stabilization of HCV-associated collapsing FSGS[51].

IgA NEPHROPATHY

Association of IgA nephropathy with HCV infection has also been reported in several reports[53-55]. Some researchers described a case of HCV-related IgA nephropathy successfully treated with IFN-α. Dey *et al*[55] reported a case of HCV-associated IgA nephropathy in which marked improvement with IFN therapy was observed.

FIBRILLARY/IMMUNOTACTOID GLOMERULOPATHY

Fibrillary-immunotactoid glomerulopathies may be associated with systemic disorders such as lymphoproliferative disorders, adenocarcinomas, connective tissue diseases and infectious diseases[56]. Six cases of fibrillary-immunotactoid glomerulopathies associated with HCV infection have been described[15,57,58]. Most of the patients with fibrillary glomerulopathy presented with hypertension, edema, microscopic hematuria and nephrotic proteinuria. All patients had detectable HCV antibody titers. Fibrillary and immunotactoid glomerulopathies are characterized by extracellular deposits of microfibrils within the mesangium and glomerular capillary walls which do not stain for Congo red[59]. Furthermore, immunofluorescence microscopy reveals IgG, especially IgG4, and C3 in the lesions[56]. On electron microscopy, fibrils with diameters of 16 to 28 nm and 33 to 45 nm were observed in fibrillary glomerulonephritis and immunotactoid glomerulopathy, respectively[60].

DIABETIC NEPHROPATHY

A link between HCV infection and type 2 diabetes mellitus (DM) has been proposed. The prevalence of HCV positivity in type 2 diabetic population ranges between 1.7% and 12.1%[61]. Mehta *et al*[62] reported that HCV-infected patients older than 40 years of age had 3 times higher risk for type 2 DM than the people without HCV infection. A high prevalence of HCV infection has also been observed in patients with diabetic nephropathy[63]. After kidney transplantation, HCV infection has been identified as a predictive factor for DM[64]. Gentil and coworkers[65] found that patients with HCV positivity had higher prevalence of DM after kidney transplantation. However, a large cohort study of 33479 kidney transplant recipients included in the United States Renal Data System showed no association between HCV and diabetic nephropathy as a cause of ESRD[66]. The incidence of DM following kidney transplantation was found to be higher with the use of donor HCV-positive kidneys compared to the other types of post-transplant HCV positivity[67].

In the previous study by our group, we found that HCV infection was independently associated with post-transplant DM[64]. On the other hand, auto-antibodies such as anti-glutamic acid decarboxylase (anti-GAD) and islet cell antibody (ICA) were not increased in patients with HCV infection, suggesting that non-immunological mechanisms were responsible for post-transplant DM.

It was suggested that impaired insulin sensitivity and beta-cell dysfunction contributed to glucose intolerance and insulin resistance in HCV-positive patients[68]. HCV core protein directly reduces the expression of insulin receptor substrate proteins (IRS) 1 and 2[69]. In study by Aytug *et al*[70], HCV infection resulted in a 2- to 3-fold increase in insulin receptor and IRS-1 compared to subjects without HCV infection. However, insulin-stimulated IRS-1 tyrosine phosphorylation was found to be decreased 2-fold in HCV-infected subjects. In the study by Shintani *et al*[71], insulin resistance was investigated in mice that were transgenic for HCV core protein. These mice had increased serum insulin and glucose levels in response to insulin injection. In this study, tumor necrosis factor-α has been considered to cause insulin resistance through inhibition of tyrosine phosphorylation of IRS-1 and IRS-2.

Insulin resistance and hyperinsulinemia cause increased intrarenal production of insulin-like growth factor-1 and transforming growth factor-β and the expression of angiotensin Ⅱ receptors in mesangial cells, thus enhancing the harmful effects of angiotensin Ⅱ in the kidney. Furthermore, increased endothelin-1 and oxidative stress and reduced nitric oxide synthesis contribute to renal injury in the setting of insulin resistance[72]. In patients with diabetic nephropathy, the slope of serum creatinine was significantly greater in HCV-positive patients compared to that of HCV-negative patients[58]. Hence, HCV infection was suggested to be related to the progression of diabetic nephropathy[73].

KIDNEY TRANSPLANTATION AND HCV INFECTION

The most frequently reported HCV-associated adverse events after kidney transplantation are chronic allograft dysfunction, HCV-related glomerulopathy and posttransplant DM[74]. After kidney transplantation, renal diseases that have been reported in HCV-infected patients include the recurrent or *de novo* MPGN, MN, minimal change

disease, renal thrombotic microangiopathy, FSGS, acute and chronic transplant glomerulopathies (CTG)[50,75,76]. MPGN was found to be the most common glomerulopathy after kidney transplantation in patients with HCV infection, at rates ranging from 5% to 54%[75]. Poorer patient and graft survival and higher proteinuria were reported to be associated with the *de novo* HCV-related nephropathy after kidney transplantation[66,76-78].

The presence of anti-HCV antibodies before kidney transplantation was found to be a predictive factor for the occurrence of proteinuria and reduced graft survival after the transplantation[77]. Cosio *et al*[79] also reported that patients with CTG had higher prevalence of HCV positivity. However, in another study, the prevalence of CTG was found similar in biopsies of HCV-positive and HCV-negative patients[14].

Zylberberg *et al*[80] investigated the impact of kidney transplantation on the course of HCV infection. They retrospectively compared 28 HCV-positive renal transplant recipients with 28 HCV-negative controls. HCV-positive patients had no antiviral therapy. The liver histology worsened in renal transplant recipients but minimally changed in controls in the 7 years of follow-up. Kidney transplantation may have adverse effects on the progression of liver disease in HCV-positive patients.

In the study by Mathurin *et al*[81], 834 renal transplant patients with positive serologic markers for hepatitis B virus and/or HCV were included. A total of 706 patients were HCV positive. At 10 years, among patients with HCV screening, the presence of HCV antibodies was found to be an independent prognostic value in patient survival. The case-control study showed that anti-HCV positivity was independently associated with both patient and graft survivals.

RENAL DISEASES AFTER LIVER TRANSPLANTATION

Renal diseases may have adverse effects on the outcome of liver transplantation in HCV-infected patients. MPGN and cryoglobulinemia have been previously reported after liver transplantation in patients with chronic HCV infection[82,83]. All of these patients had preexisting detectable cryoglobulins before the transplantation. This finding was also confirmed by the study by Abrahamian *et al*[82]. They found that the prevalence of cryoglobulinemia was higher in HCV-positive patients compared to HCV-negative patients after liver transplantation (19% *vs* 0% respectively). In the study by Kendrick *et al*[83], slope of creatinine clearance was found to be similar in HCV-positive and HCV-negative liver transplant recipients. However HCV-positive patients were significantly more likely to have proteinuria when compared to HCV-negative patients. MPGN was also found to be more common in HCV-positive patients. Chronic kidney disease (CKD) may be considered to be a complication of liver transplantation. In a study performed on non-renal transplant patients, presence of HCV infection was found to be an independent risk factor for CKD together with DM and hypertension[84]. If ESRD develops, kidney transplantation may be successfully performed to the HCV-positive liver transplant patients[85].

TREATMENT OF HCV-ASSOCIATED GLOMERULOPATHIES AND CRYOGLOBULINEMIC RENAL DISEASE

Three approaches may be suggested for the treatment of the HCV-associated glomerulopathies and cryoglobulinemic renal disease: 1- antiviral therapy to prevent the further direct damage of HCV on kidneys and synthesis of immune-complexes; 2- B-cell depletion therapy to prevent formation of immune-complexes and cryoglobulins; and 3- nonspecific immunosuppressive therapy targeting inflammatory cells to prevent the synthesis of immune-complexes and to treat cryoglobulin associated vasculitis[34,40].

Proteinuria and hypertension are the main clinical features of HCV-associated glomerulopathies, thus renoprotection with anti-hypertensive and anti-proteinuric agents such as renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors and/or angiotensin Ⅱ receptor blockers) should be applied as needed[86].

In the very recent Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Glomerulonephritis, in patients with moderate proteinuria, stable renal functions and mild to moderate histological lesions at renal biopsy, anti-HCV therapy is advised to be started with PEG-IFN-α plus ribavirin[87-89]. However in patients with nephrotic-range proteinuria and/or progressive kidney injury and other extra-renal manifestations such as cutaneous ulcers, intestinal ischemia, severe neuropathy or alveolar hemorrhage, immunosuppressive therapy with cyclophosphamide (2 mg/kg per day for 2-4 mo), rituximab (375 mg/m^2 once a week for 4 wk), steroid pulses (0.5-1 g/d for 3 d) and plasmapheresis (3 L of plasma thrice weekly for 2-3 wk) should be administered[87]. Since IFN-α may exacerbate cryoglobulinemic vasculitis, it should be started only after the acute phase of the disease is controlled with immunosuppressive agents[90]. For HCV-associated glomerulopathy with CKD Stages 3-5 (not yet on dialysis), monotherapy with PEG-IFN-α was suggested with doses adjusted to the level of kidney function.

HCV genotype should be determined before anti-HCV therapy because patients infected by genotype 1 and 4 have a poor response to IFN therapy which may also predict a poor renal response[91]. The recommended duration of therapy according to some experts is 1 year[87]. However treatment duration should be adjusted for HCV genotype and virological response to treatment and it may vary from 24 to 72 wk[92].

Since there is no standardized classification of severity for HCV-related cryoglobulinemic glomerulonephritis, recommendations for the management of this disease are based on small uncontrolled studies, case reports, and

experts' opinions.

The recommended therapeutic regimen for cryoglobulinemic vasculitis consists of a 48-wk course of once-weekly Peg-IFN-α-2a (180 μg) or Peg-IFN-α-2b (1.5 μg/kg) combined with 1000-1200 mg of daily ribavirin for patients with genotypes 1 and 4, and a 24-wk course of Peg-IFN-α combined with 800 mg/d of ribavirin for patients with genotypes 2 or 3[93].

Anti-viral agents

The antiviral therapy in HCV-associated glomerulopathies is administered to eliminate the virus and thus reduce the generation of HCV-related immune complexes. The best parameter for long-term prognosis is SVR. Combination therapy (ribavirin + IFN-α) has the most favorable outcome with higher SVR and lower proteinuria. In a recent meta-analysis investigating the efficacy and safety of antiviral *vs* immunosuppressive therapies (corticosteroids ± cyclophosphamide) for the treatment of HCV-associated glomerulopathies, IFN-α was found to be more successful at lowering proteinuria[94]. However, both treatment groups failed to improve renal dysfunction.

Combination therapy with IFN and ribavirin has been found to be successful in the treatment of HCV-associated glomerulopathies[95]. Alric *et al*[96] reported that long-term therapy of HCV-related cryoglobulinemic MPGN with combination anti-viral treatment was associated with a SVR in 67% of patients. After treatment, proteinuria and cryoglobulin levels decreased significantly.

In the meta-analysis by Feng *et al*[97], antiviral treatment based on IFN-α was found to decrease proteinuria in HCV-positive CKD patients. The decrease in proteinuria following antiviral therapy was associated with HCV-RNA clearance. Serum creatinine levels were not significantly decreased with anti-viral treatment; however stabilization of serum creatinine was achieved. Patients receiving combination therapy with IFN plus ribavirin achieved a higher SVR than those with IFN monotherapy regardless of HCV genotype.

In a recent study investigating the efficacy and safety of IFNα/ribavirin/protease inhibitor combination in HCV-induced-MC, telaprevir and boceprevir were found to be highly effective[98]. Moreover, all patients with kidney involvement improved significantly. However telaprevir and boceprevir should be used carefully in patients with a high risk of renal impairment because very recently, these drugs were found to be related to a significant decrease in glomerular filtration rate[99].

IFN-α has been reported to exacerbate proteinuria in some patients with glomerulopathies[100]. IFN therapy has been used for the treatment of various diseases and causes proteinuria as an adverse effect in approximately 20% of subjects[101]. However, the mechanism of proteinuria induced by IFN is not fully known. One of the immunologic effects of IFN is the alteration of the balance of T helper cells type 1 (Th1) and T helper cells type 2. IFN-induced Th1-dominant immune response may be involved in the exacerbation of underlying glomerulonephritis. In a study by Kimmel *et al*[102], after IFN therapy, immune complexes containing IFN were found in the circulation and renal tissue in a patient with MPGN. Foot process effacement may also be a factor in the pathogenesis of IFN-induced proteinuria[100].

Nonspecific immunosuppressive agents

Cyclophosphamide is indicated in HCV-associated glomerulopathies because it is an effective agent for inhibition of B lymphocytes and thus cryoglobulin production. Cyclophosphamide has been used successfully in this patient population; however the possibility of flare up of HCV infection and increase in HCV RNA levels should always be kept in mind[103].

Mycophenolate mofetil (MMF) is more selective than cyclophosphamide in inhibiting lymphocyte proliferation and functions. MMF may be a less toxic alternative to cyclophosphamide for the induction of remission in mixed cryoglobulinemic vasculitis[104].

In the presence of severe mixed cryoglobulinemia manifestations, corticosteroids may be used at high oral doses (*e.g.*, prednisone 0.5-1.5 mg/kg per day) or intravenous pulses (methylprednisolone 0.5-1.0 g/d for 3 d followed by oral prednisone). However, corticosteroids may also favor HCV replication and worsen liver disease.

B-Cell depletion therapy- rituximab

Rituximab is a B-cell depleting monoclonal antibody against CD-20. It interferes with the synthesis of cryoglobulins and monoclonal IgM. It has also been used in the treatment of HCV-associated glomerulopathies with or without cryoglobulinemia[105,106]. Such patients had a significant decrease in proteinuria with the rituximab therapy[106]. In a prospective controlled trial performed on patients with HCV-associated mixed cryoglobulinemic vasculitis, combination therapy with rituximab plus PEG-IFN-α-2b/ribavirin was found to be superior to PEG-IFN-α-2b/ribavirin in terms of the rate of complete response to kidney disease (81% *vs* 40%)[107]. In an observational study performed on patients with HCV-associated vasculitis, rituximab was administered without antiviral therapy and HCV RNA levels remained stable[108]. Rituximab seemed to be safe in patients with HCV infection in other studies[109]. It should be noted that rituximab may rarely form a complex with IgM-RF and lead to increased cryoprecipitation[110]. Thus, to prevent this potential severe side effect, rituximab should be administered after plasma exchange in patients with high baseline cryoglobulin levels[94]. When compared to cyclophosphamide, rituximab may be suggested to be the prefered agent in the treatment of HCV-associated glomerulopathies because it is at least as efficient as cyclophosphamide in inhibiton of the synthesis of immune-complexes and cryoglobulins, and it does not seem to cause flare of HCV infection[109].

Plasmapheresis

Plasma exchange therapies are performed in the acute

phase of the disease to remove circulating immune-complexes and cryoglobulins from the plasma[111]. It is suggested that removing immune-complexes from the circulation may also retard the accumulation of the immune-complexes into the kidney. The usual dose of plasmapheresis in the treatment of HCV-associated glomerulopathies is the exchange of 3 L of plasma 3 times/wk[31]. Plasmapheresis is especially effective in the setting of rapidly progressive glomerunephritis[112]. It should be combined with immunosuppressive therapies to prevent the re-accumulation of immune-complexes and cryoglobulins.

Potential future therapies

Low-dose interleukin 2 (IL-2) has been recently suggested as an alternative treatment for HCV-associated mixed cryoglobulinemic vaculitis[113]. IL-2 is hypothesized to promote regulatory T cell (Treg) survival and function. In this prospective open-label, phase 1-phase 2a study, 10 patients with HCV-induced vasculitis refractory to current treatment modalities received low-dose IL-2. Reduction in cryoglobulinemia and improvement of vasculitis were observed in most of the patients. Furthermore it led to a prominent inhibition of inflammation and oxidative stress mediators. These favorable effects of IL-2 were considered to be related to Treg recovery.

Management of anti-viral therapy in patients with impaired kidney function

The kidneys are important in the catabolism and clearance of both IFN-α and ribavirin, thus patients with reduced kidney function have increased risk for the side effects of these drugs[89]. Actually there is not much information about the treatment of HCV infected patients with GFR < 60 mL/min but not on dialysis. The suggested doses, based on expert opinion, are PEG-IFN-α-2b 1 μg/kg per week or PEG-IFN-α-2a 135 μg/wk, together with ribavirin 200-800 mg/d in two divided doses[88].

Ribavirin may cause hemolytic anemia especially in patients with reduced renal functions. Renal function should be evaluated in all patients before ribavirin is administered. Patients with renal impairment should be monitored for the development of hemolytic anemia, and the daily dose of ribavirin should be adapted to the glomerular filtration rate[34]. If the serum creatinine level increases to more than 2.0 mg/dL, PEG-IFN and ribavirin must be discontinued[114]. In the study by Kamar *et al*[115], liver fibrosis was found to be accelerated in renal transplant patients treated by ribavirin probably due to iron deposition in liver induced by ribavirin-associated chronic hemolysis. Similar findings were also observed in liver transplant patients after one year of ribavirin monotherapy[116]. Ribavirin use in patients with GFR < 50 mL/min per 1.73 m^2 is not recommended in guidelines[117] although recent data has emerged supporting its cautious use in patients with decreased GFR in a well-monitored setting[87]. However, despite monitoring, ribavirin-induced hemolytic anemia may occur[95]. Taribavirin, a prodrug of ribavirin, does not significantly accumulate in erythrocytes, and has shown an antiviral efficacy similar to that of ribavirin, with a lower occurrence of anemia[118].

Treatment of HCV infection after kidney transplantation

Antiviral therapy after kidney transplantation is not generally preferred because IFN has limited efficacy and increases the risk of renal graft rejection in 15%-64% of cases by inducing T lymphocytes[119]. However in the open pilot study by Pageaux *et al*[120], PEG-IFN-α-based treatment achieved significant SVR with a low risk of renal dysfunction in kidney transplant patients.

HCV RNA levels are known to increase in kidney transplant patients after anti-thymocyte globulin[75]. Among calcineurin inhibitors, cyclosporin was found to specifically inhibit HCV in hepatocytes; however this effect was not observed with tacrolimus[121]. Furthermore, progression of liver fibrosis was less severe in kidney transplant patients treated with cyclosporin[80,115]. Thus, cyclosporin may be a better choice as a component of the immunosuppressive therapy in kidney transplant patients with HCV infection.

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