More than 170 million people worldwide are chronically infected with the hepatitis C virus (HCV), which is responsible for over 1 million deaths resulting from cirrhosis and liver cancers. Extrahepatic manifestations are also relevant and include mixed cryoglobulinemia, lymphoproliferative disorders, and kidney disease. HCV infection is both a cause and a complication of chronic kidney disease, occurring largely in the context of mixed cryoglobulinemia. This infection also represents a major medical and epidemiologic challenge in patients with end-stage renal disease on renal replacement therapy with dialysis or transplantation. In these settings the presence of HCV correlates with higher rates of patient mortality than in HCV-negative subjects on dialysis or undergoing kidney transplant. The major concern is the lack of safe and effective drugs to treat HCV-infected patients with chronic kidney disease. Unfortunately, there are no large-scale clinical trials in this population, especially those receiving renal replacement therapy, so that strong evidence for treatment recommendations is scant. This review article provides the readers with the most recent insights on HCV infection both as cause and complication of chronic kidney disease, discusses pitfalls and limitations of current therapies, and reports on preliminary experience with novel therapeutic agents, as well as directions for future research.


Hepatitis C Infection and Chronic Renal Diseases

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HCV Diagnosis in CKD Patients

HCV infection results in an increase in serum alanine aminotransferase (ALT), a nonspecific marker of liver damage. The diagnostic value of ALT measurement to assess acute or chronic HCV infection is, however, rather weak in CKD patients, particularly in those on renal replacement therapy with hemodialysis or kidney transplant, since normal aminotransferase levels have been often reported in this patient population (4). This inconsistency has been ascribed to vitamin B6 deficiency, presence of uremic toxins, or UV-absorbing components in the blood that could alter the transaminase detection (4,5). Moreover, serum ALT level does not correlate with the viral load or with tissue liver injury, further indicating the shortcoming of this tool to monitor HCV infection.

Detection of anti-HCV antibodies by third-generation enzyme immunoassay allows rare false-negative results in dialysis patients (6,7) but does not distinguish acute and chronic HCV-infection. Nevertheless, in enzyme immunoassay-positive patients HCV infection should be confirmed by HCV RNA assay in a blood sample. In hemodialysis patients, samples for HCV RNA detection should be collected before the dialysis procedure to avoid the risk of false-positive PCR results because of the presence of heparin in the blood (8). Quantitative determination of viral load is also useful to provide prognostic information about the infection because patients with high initial HCV RNA levels benefit more from 48-wk treatment but have greater risk of relapse (1). Remarkable value is also attributed to HCV genotyping since genotypes 1, 4, 5, and 6 are more resistant to IFN treatment and need longer courses of therapy (1).

Liver biopsy provides key information on the extent of HCV-associated hepatic disease, but requires caution in CKD because of the potential low risk of bleeding complications, especially in patients with chronic kidney diseases (9,10). Transjugular bi-
oppsy seems safer. As alternatives to liver biopsy, noninvasive methods have been proposed, including fibrotest, which is an algorithm combining the results of serum tests of α₂-macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, gamma glutamyltranspeptidase, and alanine aminotransferase to assess the level of fibrosis and necroinflammatory activity (11). This test showed similar diagnostic performance in hemodialysis and renal transplant patients with HCV infection (12). Other noninvasive biomarkers, such as hyaluronic acid, have been proposed so far. However, they failed to predict or rule out hepatic fibrosis and/or cirrhosis when applied in transplant patients with HCV (13).

Mechanisms of HCV-Induced Kidney Injury

Renal parenchyma expresses CD81 and SR-B1 receptors that allow HCV binding to the cell surface and endocytosis (14). Indeed, HCV RNA and related proteins have been found in mesangial cells, tubular epithelial cells, and endothelial cells of glomerular and tubular capillaries (15,16). The presence of HCV-related proteins in the mesangium was associated with higher proteinuria (16), possibly reflecting direct mesangial injury by HCV infection.

A role in HCV-associated renal injury has been recently suggested for toll-like receptors (TLRs), primary proteins expressed on immune and nonimmune cells as key components of the innate immune system (17). TLRs recognize molecular patterns associated with microbial pathogens and induce an immune response (17). Renal biopsy findings of increased expression of TLR3 specifically in microdissected glomeruli of patients with HCV-related membranoproliferative glomerulonephritis (MPGN), but not non-HCV MPGN (18), suggest a link between TLR3 and HCV-related glomerular disease. TLR3 is expressed preferentially in the mesangial cell target of HCV-related MPGN. However, while HCV is a single strain RNA virus, TLR3 recognizes double-strand RNA, and the implications of these findings in disease pathophysiology remain to be established.

Much more is known about kidney injury due to systemic immune response to HCV infection that is mediated by cryoglobulins (a group of globulins with the common property of precipitating from cooled serum), HCV-antibody immune complexes, or amyloid deposition (14). Persistence of HCV leads to chronic overstimulation of B-lymphocytes and production of mixed cryoglobulins mainly composed of a polyclonal immunoglobulin (Ig), either IgG or IgM, bound to another Ig that acts as an anti-rheumatoid factor (RF) (19–22).

Cryoglobulins are deposited in the mesangium during their trafficking in the glomerulus. Their nephrotoxicity is attributed to particular affinity of the IgM-κ-RF for cellular fibronectin in the mesangial matrix. Cryoglobulins can also be deposited in the glomerular capillaries as eosinophilic material that stains densely with antiserum to IgM, C3, and fibrin by immunofluorescence (14). This is usually associated with histologic signs of vasculitis and downstream fibrinoid necrosis of the glomeruli. Cryoglobulins may also induce endothelitis via anti-endothelial antibody activity and complement activation leading to overexpression of VCAM-1 and subsequent platelet aggregation (14).

Another possible mechanism underlying HCV-related kidney injury is nonimmunologically mediated. HCV-positive patients with and without cirrhosis have elevated levels of fasting serum insulin and insulin resistance, and higher prevalence of diabetes (reviewed in (23)). HCV core protein directly reduces expression of insulin receptor substrate proteins (IRS) 1 and 2 (24), responsible for metabolic effects of insulin, and promotes activation of IRS-1 and high expression of TNF-α at least in hepatic cells (25). Insulin resistance and hyperinsulinemia cause excess intrarenal production of IGF-1 and TGFβ, thus promoting proliferation of renal cells, and upregulate the expression of angiotensin II type 1 receptors in mesangial cells, thus enhancing the deleterious effects of angiotensin II in the kidney. This setting also leads to excess local production of endothelin-1, reduced endothelial synthesis of nitric oxide, and increased oxidative stress (26).

HCV-Related Glomerulonephritis

Clinical Manifestations and Natural History

Glomerulonephritis develops many years, often decades, after initial infection with HCV. The most common HCV-related nephropathy is MPGN, usually in the context of cryoglobulinemia. The majority of cryoglobulinemic HCV-infected patients have either no symptoms or nonspecific clinical manifestations. The triad of purpura, asthenia, and arthralgia is evident in nearly 30% of cases (21). Cryoglobulinemic vasculitis, predominantly involving the small vessels, is observed in less than 10% of patients (22). The most frequently affected tissues/organisms are skin, nerves, and kidney. Renal involvement is reported in one-third of cryoglobulinemic patients (3), but the reasons for renal disease development in a selective group of patients remains unknown. Renal signs of cryoglobulinemia include proteinuria and microscopic hematuria with mild to moderate renal insufficiency (27). Glomerular disease may manifest acutely as oliguric acute renal failure in 5% of cases (3). The majority of patients develop hypertension, often severe and difficult to control. Renal biopsy shows a pattern of MPGN, with typical immune complex deposition in glomeruli (27,28). Inflammatory cells—both mononuclear cells and polymorphonuclear leukocytes—infiltrate the glomerular capillaries. Mesangial matrix expansion, splitting of capillary basement membranes, and intracapillary globular accumulation of eosinophilic material representing precipitated immune complexes or cryoglobulins can be documented (3). Usually, the diagnosis of HCV-related MPGN is made by positive tests for serum HCV antibodies and HCV RNA. ALT levels are increased in 70% of patients, and the majority have low serum concentrations of complement components (C1q, C4, and C3) (3).

Besides MPGN, other forms of glomerular disease have been associated with HCV infection, which include IgA nephropathy, postinfectious glomerulonephritis, membranous nephropathy, thrombotic microangiopathies, focal and segmental glomerulosclerosis (3), and fibrillary or immunotactoid glomerulopathy (29). The course of these HCV-associated
nephropathies is characterized by remission and relapsing phases.

The long-term outcome of HCV-associated nephropathies remains ill-defined. In a recent retrospective cohort study involving over 470,000 adult veterans, patients with HCV infection were more likely to develop ESRD (4.3 per 1000 person-year) than HCV-seronegative patients (3.1 per 1000 person-year) (30). Moreover, in patients with an estimated glomerular filtration rate (GFR) ≤30 ml/min per 1.73 m², the presence of HCV was associated with a nearly threefold higher risk of ESRD. These findings were confirmed by a subsequent cross-sectional study showing that HCV-positive patients had a 40% higher likelihood for developing renal insufficiency—defined as serum creatinine levels ≥1.5 mg/dl—compared with seronegative subjects (31). Beside the risk of renal disease progression, the overall prognosis for patients with HCV-related nephritis is poor because of a high incidence of co-infections and cardiovascular disease (32).

**Treatment of HCV-Related Glomerulonephritis**
Hypertension, proteinuria, and progressive renal failure are the main clinical manifestations of HCV-associated CKD. Thus, renoprotection with blood pressure-lowering and antiproteinuric agents—shown effective in other proteinuric chronic nephropathies (33,34)—must be applied. Diuretics, renin–angiotensin system inhibitors (either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), and eventually lipid-lowering agents, have been proven to be beneficial in HCV patients with CKD (35).

Nevertheless, given the link between HCV infection and immune response targeting the glomerulus, antiviral and immunosuppressive therapies have also been used in these patients (36). The antiviral therapy in HCV-positive patients with CKD is aimed at eliminating the virus and reducing the generation of HCV-related antibodies and immune complexes. Current treatment options for HCV infection are reported in Table 1. Several indicators of therapy efficacy have been proposed. The most reliable for long-term prognosis is sustained virologic response (SVR)—HCV RNA clearance from serum at least 6 mo after cessation of therapy.

It should be emphasized, however, that SVR to treatment of HCV infection may depend on a series of cofactors and comorbidities (37,38). Therapeutic response to antiviral therapy has been shown to be significantly influenced by the genotype of HCV. For example, SVR occurs in 65 to 90% of patients receiv-

<table>
<thead>
<tr>
<th>Table 1. Current Antiviral HCV Treatment Options for HCV</th>
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<tbody>
<tr>
<td><strong>IFN-α</strong></td>
</tr>
<tr>
<td>IFN-α is a nonglycosylated serum protein produced by immune cells in response to foreign antigen exposure. IFN is filtered by the glomerulus and reabsorbed by the proximal tubular cells, where it undergoes proteolytic degradation. Thus, accumulation of IFN occurs in patients with renal dysfunction. Several forms of IFN are available for therapeutic use, such as α-2a, α-2b, α-n1. The main side effects associated with IFN include influenza-like symptoms, hematologic abnormalities, depression, confusion, anorexia, diarrhea, dermatitis, alopecia, increased infection rate, uncontrolled hypertension, heart failure, and pericarditis (60).</td>
</tr>
<tr>
<td><strong>Pegylated IFN-α (PEG-IFN)</strong></td>
</tr>
<tr>
<td>A long-acting IFN-α, namely pegylated IFN or peginterferon, produced by the covalent attachment of polyethylene glycol to the IFN molecule, has been developed. Two PEG-IFN formulations are currently approved for treatment of HCV: alfa-2a (PEG-IFN alfa-2a) and alfa-2b (PEG-IFN alfa-2b). Given the increased half-life as compared with conventional IFN, PEG-IFN formulations could be administered weekly. PEG-IFN alfa-2a is metabolized in the liver and kidneys, while PEG-IFN alfa-2b is cleared only by the kidneys. These pharmacokinetic differences account for a slower onset of side effects with PEG-IFN alfa-2a than alfa-2b in the presence of renal dysfunction (128). Adverse events with PEG-IFN therapy are the same as those of IFN.</td>
</tr>
<tr>
<td><strong>Ribavirin (RBV)</strong></td>
</tr>
<tr>
<td>RBV is a member of the nucleoside antimetabolite drugs that interfere with duplication of HCV RNA. Bioavailability of oral RBV is increased by 70% in coadministration with a high-fat meal. The principal route of elimination for RBV and its metabolites is the kidney. In patients with GFR less than 30 ml/min the blood area under the curve of RBV is threefold higher than in those with normal renal function. Thus, daily dosage of RBV in patients with chronic kidney disease should be adapted to GFR value and predicted according to specific formulas (129,130). RBV is not removed by hemodialysis (131). The main side effect of RBV is hemolytic anemia related to the high concentration of the drug in red blood cells when the renal clearance is markedly reduced. Indeed, ribavirin is taken up by an active cell surface transporter and phosphorylated to ribavirin triphosphate. Erythrocytes are, however, unable to dephosphorylate or secrete ribavirin triphosphate. As a result, the latter accumulates within the cell and adenosine triphosphate depletion occurs, leading to cell membrane damage. Injured red cells are then removed from the circulation by spleen cells (3). RBV is teratogenic, thus requiring reliable methods of contraception during treatment.</td>
</tr>
</tbody>
</table>
ing IFN-α and ribavirin and infected with viral genotypes 2 and 3, but in only 30 to 50% of those with HCV genotype 1 (39–42).

Regarding specifically the effect of antiviral therapy in HCV-associated glomerulonephritis, the results are very heterogeneous (Table 2). More favorable treatment outcomes, as indicated by higher SVR and lower relapse rate of proteinuria, have been achieved recently by combined therapy with ribavirin and IFN or pegylated (PEG)-IFN. Absence of positive creatinine level dynamics in most studies could be explained by the fact that the majority of patients had either not very high levels of creatinine, or late initiation of therapy and irreversible morphologic changes. There is only one case report (43) of fludarabine therapy in a patient with HCV-cryoglobulinemic glomerulonephritis, showing renal disease remission for 2 yr after treatment. Although some results of antiviral therapy in HCV patients are encouraging, a close monitoring (possibly through blood drug measurement) is needed for patients with renal dysfunction to avoid the risk of drug overdosing and life-threatening side effects (see Table 1).

Patients with mixed cryoglobulinemia, with or without renal involvement, have been treated in the past, either by plasma exchange to remove circulating cryoglobulins or by immunosuppressive drugs (steroids or cyclophosphamide) to suppress antibody and cryoglobulin production (44,45). Uncontrolled studies show that steroids often allowed remission of the acute phase of the disease, but were poorly tolerated (46,47). Anyway, caution should be taken using immunosuppressive drugs in HCV-associated glomerulonephritis because of concern regarding possible further viral replication (48). A recent meta-analysis (49) of controlled clinical trials comparing the efficacy and safety of antiviral versus immunosuppressive therapy (corticosteroids alone or in combination with cyclophosphamide) in patients with HCV-associated glomerulonephritis showed that proteinuria decreased more (odds ratio 3.86) after IFN therapy (3 MU thrice weekly for at least 6 mo) (46,47). However, both treatments failed to significantly improve renal dysfunction. Of note, in all patients with proteinuria reduction HCV RNA clearance was documented at the end of IFN therapy (49). Anecdotal experience is also available with the cryoprecipitate apheresis in patients with HCV-associated immune complex nephritis refractory to antiviral and immunosuppressive therapies (50).

For patients unresponsive to treatment with steroids or other immunosuppressants, the administration of the novel immunosuppressant rituximab has been recently proposed (51). This human–mouse chimeric monoclonal antibody, which selectively depletes B cells by binding to the CD20 cell surface antigen (52), has a marked antiproteinuric effect in patients with idiopathic membranous nephropathy and nephritic syndrome (53). So far, only case series and case reports have been published of rituximab therapy in HCV-associated mixed cryoglobulinemia (51). Among them, 22 patients with renal involvement were treated with two to six weekly doses of rituximab (375 mg/m²) with remarkable reduction in urinary protein excretion rate and tendency to stabilize the renal function in most cases (51). Overall, the treatment was safe, although in some patients the HCV viremia level was increased, while in others it was unchanged or even decreased. This is confirmed by the recent observation in 16 patients with severe refractory HCV-related mixed cryoglobulinemia vasculitis; rituximab combined with peginterferon 2b and ribavirin represents an effective and safe therapeutic option (54). However, prospective randomized controlled trials are required to definitely establish the efficacy and safety of rituximab compared with antiviral therapy or conventional immunosuppressants in HCV-positive patients with renal disease.

**HCV in Dialysis Patients**

**Natural History of HCV Infection**

Hemodialysis patients are at particular high risk for blood-borne infections because of prolonged vascular access and potential for exposure to contaminated equipment. It has been estimated that, among patients on hemodialysis, the prevalence of HCV infection varies greatly, from less than 5% to nearly 60% according to different areas of the world (4,5,55–57). Regardless of the geographic location, however, the prevalence is consistently associated with patient age and the number of transfused blood products (4). Given the introduction of routine screening and heightened attention to prevention of spread, the prevalence of HCV infection has declined in many dialysis centers, and yet it remains unacceptably high, ranging from 8% to 10% even in the most industrialized countries (3). In European dialysis centers the incidence rate for new-onset HCV infection varies from 0.4% (58) to 16.0% per year (59). Spontaneous disappearance of HCV RNA has been reported in 1% of untreated dialysis patients (60).

A recent systematic review of the published medical literature has shown that dialysis can negatively modify the course of HCV infection (61). The meta-analysis documented that in 11,589 dialysis patients the presence of anti-HCV antibodies was an independent and significant risk factor for death, mainly resulting from increased rate of liver cirrhosis and hepatocellular carcinoma. Analysis of the American database of over 13,000 maintenance hemodialysis patients has shown that HCV was associated with higher all-cause and cardiovascular mortality across almost all clinical, demographic, and laboratory groups of patients than HCV-negative subjects (62). These findings are challenged by the observation that HCV-positive patients on dialysis from the United States Renal Data System (USRDS) registry were less likely to have coronary artery disease, stroke, and peripheral vascular disease (63). However, this conclusion may have been confounded by the elimination of some important factors as covariates in the statistical analysis (64). Furthermore, the competing mortality of ESRD and hemodialysis complications may obscure the long-term consequences of HCV (65). HCV-positive patients on dialysis are more likely to have hepatitis B and HIV co-infections, as well as cirrhosis, anemia, and psychiatric disorders than those without HCV infection (63). These comorbid conditions related to HCV infection could further significantly influence the clinical outcome of patients on hemodialysis, both in the short- and long-term.
Table 2. Results of antiviral treatment of HCV-related glomerulopathy

<table>
<thead>
<tr>
<th>Author/Ref. No.</th>
<th>Patients</th>
<th>Drug Doses</th>
<th>Viral Response</th>
<th>Renal Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misiani et al. (132)</td>
<td>20, follow-up: 24 to 48 wk</td>
<td>IFN-α-2a 1.5 MU for one week and 3 MU for 23 wk thrice weekly</td>
<td>SVR N/A Viremia relapse in all patients within 1 yr</td>
<td>Nonsignificant decrease in proteinuria compared with no IFN-treated patients. S. creat. decreased</td>
</tr>
<tr>
<td>Johnson et al. (133)</td>
<td>20, follow-up: up to 18 month</td>
<td>IFN-α 3 MU for 6 to 12 mo</td>
<td>SVR 0% (EVR 30%)</td>
<td>Proteinuria reduced in patients with EVR; nephrotic syndrome recurred in 3 of 6 patients with relapsed viremia. S. creat. unchanged</td>
</tr>
<tr>
<td>Komatsuda et al. (134)</td>
<td>5, follow-up: N/A</td>
<td>IFN-α 6 · 10^2 every day for 24 wk</td>
<td>No response</td>
<td>No response</td>
</tr>
<tr>
<td>Mazzaro et al. (135)</td>
<td>7, follow-up: N/A</td>
<td>Lymphoblastoid IFN 3 MU thrice weekly for 6 mo</td>
<td>EVR 2 pt with SVR in 1 of them</td>
<td>Proteinuria decreased in 5 pt; Relapse in all patients at the end of treatment. S. creat. unchanged</td>
</tr>
<tr>
<td>Sabry et al. (136)</td>
<td>20, follow-up: N/A</td>
<td>IFN-α for 3 mo, in case of no-response addition of RBV 15 mg/kg with total duration 12 mo</td>
<td>SVR N/A; EVR in 4 pt only on IFN and in 1 on IFN + RBV</td>
<td>Proteinuria markedly reduced; S. creat. unchanged; No data on follow-up</td>
</tr>
<tr>
<td>Bruchfeld et al. (44)</td>
<td>7, follow-up: up to 24 months</td>
<td>IFN-α-2b 3 MU (n = 4) or 1.5 MU (n = 1) thrice weekly or PEG-IFN-α-2b 50 μg once a week (n = 2) RBV 200 to 800 mg daily for 24 wk to 15 mo</td>
<td>SVR 71.4% (5 pt)</td>
<td>Proteinuria markedly reduced; hematuria disappears in 6 of 7 patients; GFR improved in 3 pt and stable in others. Results stable at follow-up</td>
</tr>
<tr>
<td>Rossi et al. (137)</td>
<td>3, follow-up: 26 months</td>
<td>RBV 15 mg/kg per d for 4 mo with subsequent addition of IFN-α-2b 3 MU three times a week for 12 mo</td>
<td>SVR in all patients</td>
<td>Proteinuria decreased; stable regression of proteinuria for more than 24 mo; GFR increased</td>
</tr>
<tr>
<td>Lopes et al. (138)</td>
<td>2, follow-up: 24 months</td>
<td>IFN-α-2b 3 MU 3 times a week, and RBV 1000 mg/d for 12 mo</td>
<td>SVR in all patients</td>
<td>Proteinuria substantially decreased; on follow-up relapse of proteinuria in 1 patient at 24 mo</td>
</tr>
<tr>
<td>Alric et al. (139)</td>
<td>18, follow-up: minimum 6 mo</td>
<td>IFN (3 MU 3 times/wk, n = 14) or PEG-IFN (1.5 μg/kg per wk, n = 4) RBV 600 to 1000 mg/d for 6 to 24 mo</td>
<td>SVR 66.7%</td>
<td>Statistically significant reduction of proteinuria only in SVR responders. S. creat. unchanged</td>
</tr>
<tr>
<td>Cua et al. (140)</td>
<td>1, follow-up: N/A</td>
<td>PEG-IFN-α-2b 1.5 μg/kg per wk 44 mo (after unsuccessful treatment by IFN)</td>
<td>N/A</td>
<td>Disappearance of proteinuria</td>
</tr>
<tr>
<td>Garini et al. (141)</td>
<td>4, follow-up: 12 months</td>
<td>IFN-α 3 MU thrice weekly (n = 2) plus RBV 15 mg/kg per d or PEG-IFN-α-2a 100 μg/wk + RBV 800 mg/day (n = 1) or PEG-IFN-α-2a 80 μg/wk plus RBV 15 mg/kg per d (n = 1) for 24 to 48 wk</td>
<td>SVR in 3 of 4 patients</td>
<td>Proteinuria decreased in 3 pt at the end of therapy; proteinuria relapsed in one patient with no HCV RNA eradication</td>
</tr>
</tbody>
</table>

EVR, end-of-treatment viral response; SVR, sustained viral response; GFR, glomerular filtration rate; N/A, not available; S. creat., serum creatinine; IFN, interferon; PEG-IFN, peginterferon; RBV, ribavirin.
Treatment of HCV Infection

Greater eradication of HCV infection by antiviral therapy has been documented in hemodialysis patients than in those with normal renal function (3,4,41,42,66,67), possibly reflecting the high antiviral drug plasma levels achieved because of reduced renal clearance. Actually, the clearance of PEG-IFN is reduced by 45% in patients with ESRD (68), being mainly affected by the permeability and pore size of dialyzers (69). This accounts for the high incidence of adverse effects (including flu-like syndrome, weight loss, myelosuppression) in dialysis patients (4,70).

A meta-analysis of 24 prospective studies, including 529 HCV-positive patients on dialysis, showed that monotherapy with IFN allowed SVR in 39% of cases, but 19% of patients were withdrawn from treatment because of side effects (71). Similar efficacy results were reported in 4 trials with 116 patients given PEG-IFN monotherapy (SVR of 31%) but the drop-out rate was 27% (71). Overall, there was, however, very high between-study variability as far outcomes independent of the antiviral therapy used, possibly because of the fact that only few of them were randomized or had controlled design. This precludes any conclusions about the indication of preferably using IFN or PEG-IFN in hemodialysis patients with HCV infection.

Better SVR response to these antiviral agents can be anticipated in dialysis patients if pretreatment viral load is low, the degree of cirrhosis is moderate, and the infection results from HCV genotype other than type 1 (60).

Combination of ribavirin with PEG-IFN is considered the gold standard of therapy in HCV-positive patients with normal renal function based on SVR response up to 50 to 60% (60). Nevertheless, physicians are reluctant to use ribavirin in patients on dialysis given the fear of the drug-related side effects, particularly hemolytic anemia, that can be exacerbated in the presence of ESRD (72). Despite this contraindication in ESRD patients, the available small studies of combined treatment with ribavirin and IFN showed that SVR response was achieved in more than 50% of patients, hemoglobin level was successfully maintained by erythropoietin and iron therapy, and the drop-out rate from anemia was limited (73–79) (Table 3). Close monitoring for patients with ESRD is mandatory to avoid the risk of ribavirin overdosing. To this, a tentative safe therapeutic range of ribavirin trough plasma concentration of 10 to 15 μmol/L has been proposed (78).

The high cost of the antiviral treatment, the risk of severe life-threatening side effects, and the lack of data on the impact of therapy and SVR response on mortality would encourage

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Drug Doses</th>
<th>SVR</th>
<th>Drop-Out Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN + RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mousa et al. (73)</td>
<td>20</td>
<td>IFN-α 3 MU/wk RBV 200 mg 3 times/wk 24 wk (n = 9); 48 wk (n = 11)</td>
<td>66% in 24 wk treatment 55% in 48 wk treatment</td>
<td>0%</td>
</tr>
<tr>
<td>Tan et al. (74)</td>
<td>5</td>
<td>IFN-α-2b 3 MU 2 times/wk RBV 200 mg per day Duration N/A</td>
<td>N/A</td>
<td>40%, all due to anemia</td>
</tr>
<tr>
<td>Bruchfeld et al. (75)</td>
<td>6</td>
<td>IFN-α 3 MU 2 times/wk for 4 wk RBV 400 mg twice daily for the first 2 wk followed by 400 mg once daily for 28 wk</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>PEG-IFN + RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rendina et al. (76)</td>
<td>35</td>
<td>PEG-IFN-α-2a 135 μg/wk RBV 200 mg/d for 24 wk (HCV genotype non-1) or 48 wk (genotype 1)</td>
<td>97%</td>
<td>14%, 1 pt due to anemia</td>
</tr>
<tr>
<td>Deltenre et al. (77)</td>
<td>14</td>
<td>PEG-IFN-α-2a 180 μg/wk RBV 800 mg/wk (with individual adjustment according to hemoglobin level) for 2 mo</td>
<td>63% in 8 patients available for follow-up</td>
<td>21%, none due to anemia</td>
</tr>
<tr>
<td>Bruchfeld et al. (78)</td>
<td>6</td>
<td>PEG-IFN-α-2b 50 μg/wk (n = 4) or PEG-IFN-α-2a 135 μg/wk (n = 2) RBV loading dose of 400 mg/d was given for 1 wk followed by 200 mg/d for 48 wk (HCV genotype 1 and 4) or 24 wk (genotype 2)</td>
<td>50%</td>
<td>50%, none due to anemia</td>
</tr>
<tr>
<td>van Leusen et al. (79)</td>
<td>7</td>
<td>PEG-IFN alfa-2a 135 μg weekly RBV 200 mg every other day for 48 wk (HCV genotype 1 and 4) or 24 wk (genotype 2)</td>
<td>71%</td>
<td>0%</td>
</tr>
</tbody>
</table>

SVR, sustained viral response; N/A, not available; IFN, interferon; PEG-IFN, peginterferon; RBV, ribavirin.
selection of dialysis patients who benefit most from the antiviral drugs. Unfortunately, there are no proved criteria for such selection. Dialysis patients waiting for transplantation could be valid candidates since achievement of SVR response after antiviral therapy would reduce the risk of chronic allograft nephropathy, de novo MPGN, and development of diabetes mellitus (72,80). On the contrary, dialysis patients with short life expectancy or with complications such as diabetes mellitus or congestive heart failure should be considered with caution for antiviral therapy (72).

**HCV and Kidney Transplant**

**Natural History of HCV Infection**

HCV infection is also a major health care issue in renal transplantation. Among kidney recipients, the prevalence of HCV infection before transplantation is reported as high as 40% (46). Patient and graft survival in HCV-positive recipients is, however, lower than in HCV-negative ones (46,47,81–85). Cohort analyses from the USRDS registry showed 13% all-cause mortality in HCV-positive kidney transplant patients compared with 8.5% in HCV negative patients (82). This difference was mainly attributed to liver failure (HCV-positive, 6.1%; HCV-negative, 0.6% patients) and infections (45.5% versus 22.9%).

On one hand, the actual role of liver injury in the increased mortality of HCV-positive kidney transplant patients remains unclear. The decompensated liver disease has been suggested to contribute to the increased death rates in HCV-positive kidney recipients (86,87). On the other hand, others have shown that HCV-positive patients with mild liver injury at pretransplant histology had no or very limited progression of fibrosis in the first 5 yr after kidney transplantation (88). Moreover, liver fibrosis remained stable or even regressed in more than 50% of HCV-positive kidney recipients 10 yr posttransplant (89). These data indicate that the possible negative effect of HCV status on the survival of kidney transplant recipients may not be strictly related to severity of liver injury. Nevertheless, further investigations are needed to definitely assess the impact of the natural history of HCV-related liver fibrosis on death rate after renal transplantation.

Increased risk of death could be also attributed to higher risk of new-onset diabetes (46,90), posttransplant glomerulonephritis (84,91,92) and sepsis (93) in transplant patients with HCV infection.

Graft and patient survival are also affected by the HCV serology of donors and recipients. Rates of HCV positivity in cadaveric kidney donors vary from 1 to 12% worldwide (81). Transplant combination of HCV-positive donor and recipient showed lower graft and patient survival than in the positive-negative donor/recipient combination in most (47,94), but not all, studies (95). Although the risk of patient death is higher in the positive-positive combination, this is, however, lower than that of HCV patients remaining on dialysis (96). This suggests that the HCV-positive donor/recipient combination is not an absolute contraindication to transplantation, despite the high risk of viral reactivation (97).

**Antiviral Therapy in Kidney Transplant Recipients**

Posttransplant administration of IFN-α (1.5 to 6 MU three times weekly for 24 to 48 wk) to HCV-positive recipients with liver disease and stable renal function improved liver function in 50% of patients, and led to negative HCV RNA in 25% of cases (3,98,99).

A meta-analysis of 12 trials of IFN-based therapy in 102 kidney transplant patients (27 with combined IFN and ribavirin) showed that SVR response was very heterogeneous, ranging from 0% to 50%, and the rate of drop-out was remarkably high (0% to 100%) (100). Even in the kidney transplant settings, the SVR response to antiviral therapy depends upon the HCV genotype, HCV1 being the more resistant (101). The beneficial effect on liver disease can, however, be associated with 15% to 60% increased risk of acute cellular or vascular rejection, and the rate of graft loss may rise up to 20% (100,102,103). Graft rejection is frequently irreversible and steroid-resistant (100). Induction of cell surface expression of HLA alloantigens, intracellular cytokine gene expression, as well as increase in antibody body production by B cells are possible mechanisms through which IFN may trigger acute graft rejection (102).

However, after discontinuation of the therapy a rebound of the HCV viral load to pretreatment levels was documented (104,105). It has therefore been recommended to avoid IFN in HCV-positive renal transplant patients because of the potential to precipitate graft rejection or the relapse of infection upon drug withdrawal.

There are small studies of ribavirin monotherapy (105–109) (400 to 1000 mg/d for 6 to 24 mo) in which little or no effect was found on HCV-RNA levels despite reduction in serum ALT concentration (105,107,108). The impact of ribavirin on liver disease in these transplant patients is controversial (107,108). Worsening of liver injury at biopsy documented in some studies has been attributed to chronic hemolysis associated with ribavirin therapy that eventually leads to liver iron overload and deposition and progressive tissue fibrosis (110). More recently, a prospective study in 15 HCV-RNA-positive patients given ribavirin alone (1000 mg/d) or in combination with amantadine (200 mg/d) showed no effect on HCV viremia and liver histology (111). Of note, in most patients antiviral treatment was limited by anemia, resulting in premature drug withdrawal and eventually requiring erythropoietin therapy (111). These findings raise safety concerns with ribavirin monotherapy in HCV-positive kidney transplant recipients.

Combined therapy with ribavirin and PEG-IFN has been attempted in liver/kidney transplant recipients to cure HCV infection reactivation, and SVR response was achieved in five of eight patients (62%) without negatively affecting renal function (112–114). These reports indicate that, although the risk of graft dysfunction with IFN therapy should not be underestimated, combined ribavirin and PEG-IFN treatment could be undertaken in particular settings when potential benefits may outweigh risks.

Evidence for the efficacy of amantadine monotherapy in kidney transplantation is also scant. In eight HCV-positive
transplant recipients amantadine improved liver function profile without affecting HCV viremia or liver histology (115).

Overall, although no definite recommendation for antiviral therapy in HCV-positive transplant recipients can be derived from these small and heterogeneous studies, IFN therapy alone or in combination with ribavirin can be suggested when the benefits of therapy outweigh the risk of treatment. Nevertheless, antiviral therapy should be geared toward patients before transplantation, as the risk of the recurrence of HCV-related glomerulonephritis is reduced with an improvement of graft survival (116).

**Rituximab in Kidney Transplantation**

A preliminary report is available about the effect of rituximab on HCV infection in kidney transplant recipients (117). In seven HCV RNA-positive kidney transplant patients given rituximab for de novo cryoglobulinemia-related membranoproliferative nephropathy, HCV infection did not flare up either during or after the antibody therapy (117), suggesting the safety of treatment even in immunocompromised subjects. In a similar group of eight patients rituximab therapy led to sustained remission of de novo mixed cryoglobulinemia as documented by reduction of proteinuria and disappearance of cryoglob-

<table>
<thead>
<tr>
<th>Table 4. Suggested strategies for HCV infection treatment in CKD patients</th>
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<tbody>
<tr>
<td><strong>Patients with HCV-Associated Glomerulonephritis (Not Treated by Renal Replacement Therapy)</strong></td>
</tr>
<tr>
<td>Symptomatic treatment for all patients: diuretics, ACEI or ARA, lipid-lowering agents.</td>
</tr>
<tr>
<td>Patients with low proteinuria and stable renal function: initiation of antiviral therapy should be based on the degree of liver damage.</td>
</tr>
<tr>
<td>Patients with moderate proteinuria but progressive renal failure: only antiviral treatment (IFN or PEG-IFN combined with RBV, for 24 wk in genotype 2 and 3 or 48 wk in HCV genotype 1, 4, 5, and 6)</td>
</tr>
<tr>
<td>IFN 3 MU three times per week or PEG-IFN 1.5 μg/kg per wk</td>
</tr>
<tr>
<td>RBV daily: initial dose according to GFR with further adaptation to plasma concentration 10 to 15 μmol/L; with erythropoietin administration.</td>
</tr>
<tr>
<td>Patients with nephrotic-range proteinuria and/or progressive renal failure: Immunosuppressive plus antiviral treatment.</td>
</tr>
<tr>
<td>Rituximab: 375 mg/m² weekly for 4 wk or cyclophosphamide: 2 mg/kg per d for 2 to 4 months or Methylprednisolone pulses: 0.5 to 1 g/d for three consecutive days</td>
</tr>
<tr>
<td>Antiviral treatment (see above)</td>
</tr>
<tr>
<td>Plasma exchange in case of high cryoglobulin levels: 3 l of plasma three times per week for 2 or 3 wk</td>
</tr>
</tbody>
</table>

**Patients on Hemodialysis**

Transplant candidates and patients with long life expectancy: (IFN or PEG-IFN combined with RBV, for 24 wk in genotype 2 and 3 or 48 wk in HCV genotype 1, 4, 5, and 6) |
| IFN (3 MU) 3 times weekly or PEG-IFN-α 2a 135 μg/wk |
| RBV initial dose 200 mg daily with further adaptation to plasma concentration 10 to 15 μmol/L; with erythropoietin administration. |
| Patients with short life expectancy: initiation of antiviral therapy should be based on the degree of the liver damage. |

**Patients with Kidney Transplant**

Symptomatic treatment for all patients: diuretics, ACEI or ARA, lipid-lowering agents. |
| Patients with fibrosing cholestatic hepatitis: absolute indication for antiviral therapy. |
| Patients with de novo GN with low proteinuria, stable renal function, and moderate changes in renal morphology: initiation of antiviral therapy should be based on the degree of liver damage. |
| Patients with severe de novo GN and high risk of chronic graft failure: antiviral therapy (IFNα alone or combined with RBV, for 24 wk in genotype 2 and 3 or 48 wk in HCV genotype 1, 4, 5, and 6) |
| IFN (3 MU) 3 times weekly |
| RBV: initial dose according to GFR with further adaptation to plasma concentration 10 to 15 μmol/L; with erythropoietin administration. |
| Patients with kidney/liver transplant and HCV reactivation: combined treatment with PEG-IFN and RBV |
| PEG-IFN-α 2b 1 μg/kg per wk or PEG-IFN-α 2a 180 μg/wk |
| RBV: initial dose according to GFR with further adaptation to plasma concentration 10 to 15 μmol/L; with erythropoietin administration. |

In all patients with HCV infection blood level of glucose should be closely monitored.

Adapted from (36). For all patients decision on treatment initiation should be done after weighting of possible benefits and harms of therapy.

ACEI, angiotensin-converting enzyme inhibitors; ARA, angiotensin II receptor antagonists; GN, glomerulonephritis; IFN, interferon; PEG-IFN, peginterferon; RBV, ribavirin; MU, million units.

aNo studies with PEG-IFN.
interference processes, powerful RNA interference activity
plexes (125). Because HCV RNA is highly susceptible to RNA
cleaves the double-stranded RNA into short fragments, called
functions as a defense mechanism against viruses triggered by
First discovered in plants, RNA interference activity
ill-defined and will be a challenge for research in the future.

Maintenance Immunosuppressive Therapy in Kidney Transplant Recipients with HCV infection
Kidney transplantation is a peculiar condition whereby the most appropriate immunosuppressant needs to be chosen to prevent rejection while minimizing viral replication. Experimental studies in rats and mice (reviewed in (119)) have shown that cyclosporine A (CsA), at clinically relevant blood concentrations, inhibited the intracellular replication of HCV, an effect independent of its immunosuppressive activity. These findings were not observed with the other calcineurin inhibitor tacrolimus. However, in the clinical setting, the peculiar antiviral effects of CsA remain controversial (46,119,120), possibly underling different sensitivity of HCV virus to CsA related to polymorphisms of nonstructural HCV proteins NS5A and NS5B (121). Similarly, preliminary results in HCV-infected non-transplanted patients with lupus nephritis showed that myco-
active metabolite of mycophenolate mofetil (MMF), inhibited HCV viral replication (122). This is in line with findings of the USRDS registry of better survival in recipients of HCV-positive kidney given MMF than those on other immunosuppressive therapy (47). In a prospective study, however, HCV viremia increased after MMF administration without significant change in the serum concentration of liver en-
zymes (123).

It has also been suggested that steroids may in turn favor HCV replication (46). This is supported by findings that HCV-infected liver transplant recipients given corticosteroid pulses for acute graft rejection showed up to 100-fold increase in HCV RNA concentrations as compared with pretreatment values (48). The same applies to azathioprine and anti-CD3 antibodies (OKT3) that may enhance viral replication and progression of liver fibrosis in liver transplant patients (119).

Together, these studies indicate that the ideal immunosuppressive therapy for transplant patients infected with HCV remains ill-defined and will be a challenge for research in the future.

Perspectives of Anti-HCV Treatment
There is great interest in the attempt to treat chronic HCV infection through the delivery of HCV-specific small interference RNA. First discovered in plants, RNA interference activity functions as a defense mechanism against viruses triggered by long strands of double-stranded RNA. The enzyme dicer cleaves the double-stranded RNA into short fragments, called small interfering RNA (siRNA), which lead to specific mRNA degradation because of homology with the RNA sequence (124). RNA interference activity can also be induced in mammalian cells through the introduction of synthetic siRNA du-
plexes (125). Because HCV RNA is highly susceptible to RNA interference processes, powerful RNA interference activity could be induced against HCV using synthetic siRNA duplexes as triggers (reviewed in (126)). In vitro, transfection or electroporation of siRNA into stable HCV subgenomic replicon cells almost completely eliminates HCV replicon RNA and abolishes the detection of HCV proteins (126). Theoretically, the flexibil-
ity of siRNA therapy makes it ideal for the treatment of rapidly evolving viruses such as HCV. The viruses that escape the therapeutic effect of one siRNA owing to error replication could become responsive to a novel siRNA targeting the altered viral sequence. Although far from a definitive clinical application, this potential therapeutic option would be especially desirable for patients with renal insufficiency and HCV infection, for whom current antiviral treatment is often ineffective or associ-
ated with unacceptable drug-related toxicity.

Conclusions
HCV infection is both a cause and complication of chronic kidney disease. It may cause glomerular disease, occurring largely in the context of mixed cryoglobulinemia. This infection also represents a major medical and epidemiologic challenge both in patients on renal replacement therapy and those undergoing kidney transplantation. The presence of HCV correlated with higher rates of mortality in patients on dialysis and transplantation than HCV-negative ones. The major concern is the lack of safe and effective drugs to treat HCV-infected patients with chronic kidney disease. Unfortunately, there are no large-scale clinical trials performed in this population, so that the evidence for treatment recommendations is scant (Table 4). The recently published Kidney Disease: Improving Global Outcomes (KDIGO) statements on screening, prevention, and thera-
py of HCV patients in kidney disease could be, however, an additional useful tool (127).

Current antiviral therapies are expensive and associated with severe side effects, whereas only 20% of the patients chronically infected with HCV will develop cirrhosis. Therefore, a critical issue for clinicians is to establish who should be treated with antiviral drugs. The development of genetic tests that could reliably predict HCV-positive patients at risk of liver scarring would represent a step forward to implement therapeutic decisions.

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Disclosures
None.

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