

## Hepatitis C infection in hemodialysis patients: A review

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### Abstract

Hepatitis C virus (HCV)-related liver disease is a significant cause of morbidity and mortality in patients with end-stage renal disease (ESRD) who is treated with dialysis or kidney transplantation (KT). The survival rate for HCV-infected renal transplant recipients is better than that for HCV-infected hemodialysis patients on transplant waiting lists. Early diagnosis and treatment of HCV infection prior to KT prevents complications post-transplantation and reduces mortality. In addition to screening for anti-HCV antibodies and detecting HCV RNA, percutaneous liver biopsy is particularly valuable for assessing the stage of liver damage in HCV-infected patients, because the stage of fibrosis is important

determining optimal treatment for HCV. Studies have been demonstrated that with conventional interferon (IFN) monotherapy or pegylated IFN monotherapy are similar efficacy and safety in HCV-infected hemodialysis patients. Sustained viral responses (SVRs) with these monotherapies have ranged approximately 30% to 40%. Limited reports support the use of IFN and ribavirin combination therapy as antiviral treatment for ESRD patients or patients on hemodialysis. Ribavirin can be started at low dose and careful monitoring for side effects. Patients that show SVR after treatment are strong candidates for KT. It is also generally accepted that ESRD patients with decompensated cirrhosis and portal hypertension should be referred to the liver transplant team for consideration of combined liver-KT.

**Key words:** Hepatitis C virus; Hemodialysis; End-stage renal disease; Kidney transplantation; Hepatitis C treatment

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**Core tip:** Hepatitis C virus (HCV)-related liver disease is a significant cause of morbidity and mortality in patients with end-stage renal disease who are treated with dialysis or KT. Early diagnosis and treatment of HCV infection prior to kidney transplantation (KT) prevent complications after transplantation and reduces mortality. Issues with current mode HCV therapy include lack of tolerability and suboptimal response rates.

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### INTRODUCTION

Liver disease related to hepatitis C virus (HCV) infection

is a significant cause of morbidity and mortality in hemodialysis (HD) patients and kidney transplant recipients. In developed countries, the prevalence of anti-HCV seropositivity among patients on maintenance HD ranges between 5% and 60%. Patients on HD are at high risk for HCV, with frequency of infection several times higher than that in non-uremic patients<sup>[1]</sup>. The spread of HCV in HD units is declining, but the prevalence of HCV in HD patients remains high<sup>[1]</sup>.

Several observational studies have demonstrated a significant and independent relationship between anti-HCV seropositive status and lower survival rate in patients with end-stage renal disease (ESRD). The two major complications of HCV-related chronic liver disease are cirrhosis and hepatocellular carcinoma, and these are suspected causes of higher mortality among HCV-positive patients.

Management of HCV-positive ESRD patients is complicated. There are unknowns related to prevention of HCV spread in dialysis units, anti-viral therapy in dialysis patients, and effects of HCV infection after renal transplantation. A wide range of studies have been published on HCV in ESRD patients, but clinical evidence is lacking with respect to most of the important issues, and most existing evidence is from uncontrolled clinical trials or retrospective surveys<sup>[2-4]</sup>.

## EPIDEMIOLOGY OF HCV INFECTION

Serologic testing has clearly demonstrated that HCV infection is highly prevalent among ESRD patients and is a serious cause of increased morbidity and mortality in this group. Failures of HCV screening, excessive exposure to blood and blood products, nosocomial transmission of HCV in HD units, and long dialysis duration are the main determinants of increased risk of HCV infection in the HD patient group<sup>[5]</sup>. The worldwide prevalence of HCV infection among HD patients varies widely, with estimates ranging from 5% to approximately 60% depending on geographic location<sup>[6-9]</sup>. In 2002, the prevalence of HCV infection across HD centers of the United States was approximately 8%, nearly five times greater than that of the general population in that country<sup>[10,11]</sup>. In some European dialysis centers, the yearly incidence of HCV infection reportedly ranges from 0.4% to 16.0%<sup>[12]</sup>. In 2011, the Turkish Society of Nephrology documented 7.9% anti-HCV seropositivity and 1.7% HCV-RNA seropositivity among Turkish HD patients<sup>[13]</sup>. Introduction of stricter blood bank screening rules, widespread use of erythropoiesis-stimulating agents instead of blood transfusions, and stronger adherence to infection control practices in dialysis units have reduced the prevalence of HCV infection in the HD patient group<sup>[14]</sup>. For example, Spain observed a decline from 24% in 1992 to 9.2% in 2002<sup>[15]</sup>. Anti-HCV prevalence among patients on chronic HD in the United States decreased from 10.4% in 1995 to 7.8% (*i.e.*, 164632 Americans) in 2002<sup>[2]</sup>. A recent multicenter survey revealed that prevalence of anti-HCV

positivity for a Belgian cohort of HD patients ( $n = 1710$ ) dropped steadily from 13.5% in 1991 to 6.8% in 2000, and the same survey revealed significant drops in many other countries including France (42% to 30%), Italy (27% to 16%), and Sweden (16% to 9%)<sup>[2]</sup>.

## IMPACT OF HCV ON SURVIVAL

One study that involved the database of more than 13000 HD patients in the United States revealed that HCV infection was more strongly associated with all causes of mortality than with HCV-negative status<sup>[16]</sup>. Lee *et al.*<sup>[17]</sup> identified HCV infection as an independent risk factor for the transition from chronic kidney disease to ESRD. A meta-analysis by Fabrizi *et al.*<sup>[18]</sup> revealed that HD can negatively modify the course of HCV infection. The authors found that the estimated relative risk of liver-related mortality in anti-HCV-positive patients on HD was 1.57 times (95%CI: 1.33-1.86;  $P < 0.001$ ) than that observed for anti-HCV-negative counterparts. The authors concluded that, in HD patients, the presence of anti-HCV antibodies is an independent risk factor for death, because of increased risk of cirrhosis and hepatocellular carcinoma. Other research has shown that kidney transplantation (KT) improves the long-term survival of ESRD patients with HCV infection<sup>[19,20]</sup>. While there is considerable evidence that HCV infection threatens the success of KT, the survival of HCV-infected renal transplant recipients is better than that for HCV-infected HD patients who are on transplant waiting lists<sup>[21]</sup>. This survival advantage may reflect systemic effects of well-functioning renal allografts that is clearing uremic toxins, and may also reflect reduced inflammatory responses and oxidative stress. HCV-related deterioration of renal transplant recipients may be linked to the immunosuppressive treatment that is required after KT. This can result in flares of HCV infection and can increase liver- and kidney-related morbidity and mortality from conditions such as cirrhosis, hepatocellular carcinoma, transplant glomerulopathy, and graft dysfunction<sup>[22]</sup>.

## PREVENTION OF HCV TRANSMISSION

Health care procedures related to nosocomial infections, unsafe drug injection practices, and blood transfusions are key factors in HCV transmission. In HD facilities, the most common lapses of healthcare quality are contamination of dialysis systems, inadequate disinfection and cleaning of environmental surfaces, improper contact of health care staff with equipment and patients, and mishandling of parenteral medications<sup>[23,24]</sup>. The guidelines for preventing HCV infection in HD settings recommend fundamental infection control practices, and routine screening of HD patients for HCV. Isolating-HCV-infected patients or using dedicated machines for such patients are not advocated, except as necessary during local outbreaks<sup>[12,24]</sup>.

## DIAGNOSIS OF HCV INFECTION IN PATIENTS WITH ESRD

Infection with HCV normally leads to increased serum alanine aminotransferase (ALT), and laboratory blood testing for ALT is used to screen for liver disease in the general population. However, this test has weak diagnostic value in ESRD patients because ALT tends to be below reference range in this patient group. The potential causes of this are vitamin B6 deficiency, presence of uremic toxins, or presence of blood components that absorb ultraviolet light<sup>[25]</sup>. To detect HCV viremia in HD patients, new thresholds for serum ALT have been proposed that are less than half (approximately 0.4 to 0.45 times) the conventional threshold<sup>[26]</sup>. Serial testing of serum ALT level might be valuable for monitoring patients on HD with known HCV infection.

Enzyme-linked immunoassays (EIAs) are commonly used to detect HCV antibodies. Third-generation EIAs for anti-HCV antibody detection have high sensitivity and specificity because these tests are based on antigens in the core, non-structural 3-4-5 proteins of the virus. Screening for anti-HCV antibodies by EIA remains a simple method, but this type of test is only meaningful for ruling out HCV infection in ESRD patients in low-prevalence settings. In the ESRD patient group, the proposed interval for HCV screening *via* antibody test is 6 to 12 mo<sup>[27]</sup>.

One disadvantage of this serologic test is false-negative result, which can present challenges for distinguishing acute from chronic HCV infection<sup>[2]</sup>. In a case where HCV infection is strongly suspected but the HCV antibody EIA is negative, blood testing for HCV RNA should be done directly using polymerase chain reaction technique<sup>[28]</sup>. Detection of HCV RNA indicates HCV replication. In populations with known higher prevalence of HCV infection, a negative EIA result does not rule out HCV infection, and testing for HCV RNA is appropriate in such cases to avoid missing HCV infections<sup>[27]</sup>. When EIA reveals that an ESRD patient is anti-HCV positive, the next step is quantitative determination of viral load. This helps confirm the antibody test result and is also useful for assessing the patient's prognostic risk stratification prior to antiviral treatment<sup>[28]</sup>. There are two main reasons why blood for HCV RNA testing should be drawn prior to a dialysis procedure: (1) presence of heparin in the blood sample can lead to false-positive PCR result for HCV; and (2) a patient's HCV RNA level can decrease during the HD session (though it will return to baseline within 48 h). Adsorption of HCV to dialysis membrane, destruction of HCV particles during the HD session, and, rarely, escape of HCV into the dialysate are other reasons why a patient's HCV RNA could be falsely low<sup>[29]</sup>.

In addition to detecting HCV RNA, HCV genotyping is also required to predict response to treatment and to specify the duration and dosage of treatment. HCV genotypes 1, 4, 5, and 6 are more resistant to treatment and require longer courses of therapy. One study

identified HCV genotype 1b as the most prevalent subtype in patients receiving HD or continuous ambulatory peritoneal dialysis in Turkey<sup>[1]</sup>. In study of Perez *et al.*<sup>[30]</sup> reported findings that HCV genotype 1a was the most prevalent subtype in patients receiving HD, with genotype 1b the next most frequent, followed by genotype 3, and other less prevalent genotypes (genotypes 2, 4, and 5). This observation may reflect differences in the epidemiology of HCV infection, viral characteristics, and host factors in ESRD patients<sup>[31]</sup>.

Percutaneous liver biopsy constitutes the most reliable tool for examining the effects of HCV infection (*i.e.*, stage of liver disease) and ruling out possible other concomitant liver diseases<sup>[31]</sup>. Neither HCV RNA viral load nor liver enzymes reflect the severity of liver injury decisively<sup>[32,33]</sup>. Liver enzyme activity and quantity of HCV RNA can fluctuate during HCV infection, whereas fibrosis is progressive and largely irreversible. There is strong evidence that the stage of liver fibrosis during HCV infection predicts survival for kidney transplant candidates and for renal grafts. In addition, determining stage of fibrosis is important for planning the treatment of HCV<sup>[34]</sup>. According to one report, up to 25% of HCV-infected patients exhibit bridging fibrosis or cirrhosis on liver biopsy<sup>[31]</sup>. Presence of advanced fibrosis does not exclude a candidate from KT, but it is inevitable that such patients will develop the comorbidities and complications of portal hypertension after transplantation<sup>[35]</sup>.

Although liver biopsy is reliable tool, it has significant limitations including serious bleeding events, and sampling and interpretation errors. Coagulopathy, thrombocytopenia, platelet dysfunction, anticoagulation during HD and anti-platelet therapy all pose increased bleeding risk in ESRD patients or patients on HD. In these individuals with increased bleeding risk, a transjugular or transfemoral route for liver biopsy may be recommended. Note that even when an experienced physician performs the biopsy and an experienced pathologist interprets the findings, this gold-standard technique is associated with up to 20% error in staging liver disease<sup>[34,35]</sup>. Ahmad *et al.*<sup>[36]</sup> compared the results for 46 HD patients with chronic liver disease who underwent transjugular liver biopsy and 32 HD patients who had undergone percutaneous liver biopsy at the same institution. The authors found that both techniques obtained adequate specimens for histological diagnosis in all patients; however, the complications differed. There were no major complications in the transjugular liver biopsy group, whereas 12% of the patients in the percutaneous liver biopsy developed bleeding complications<sup>[36]</sup>. Some authors have reported the progression of HCV-related liver disease in HD patients who are on transplantation waiting lists. One study concluded that patients whose liver biopsy show Metavir fibrosis score 1 or 2 should undergo a repeat liver biopsy every 5 years, whereas those with Metavir score 3 should be followed more intensely, with biopsies every 3 years<sup>[14]</sup>.

There are also novel non-invasive techniques for

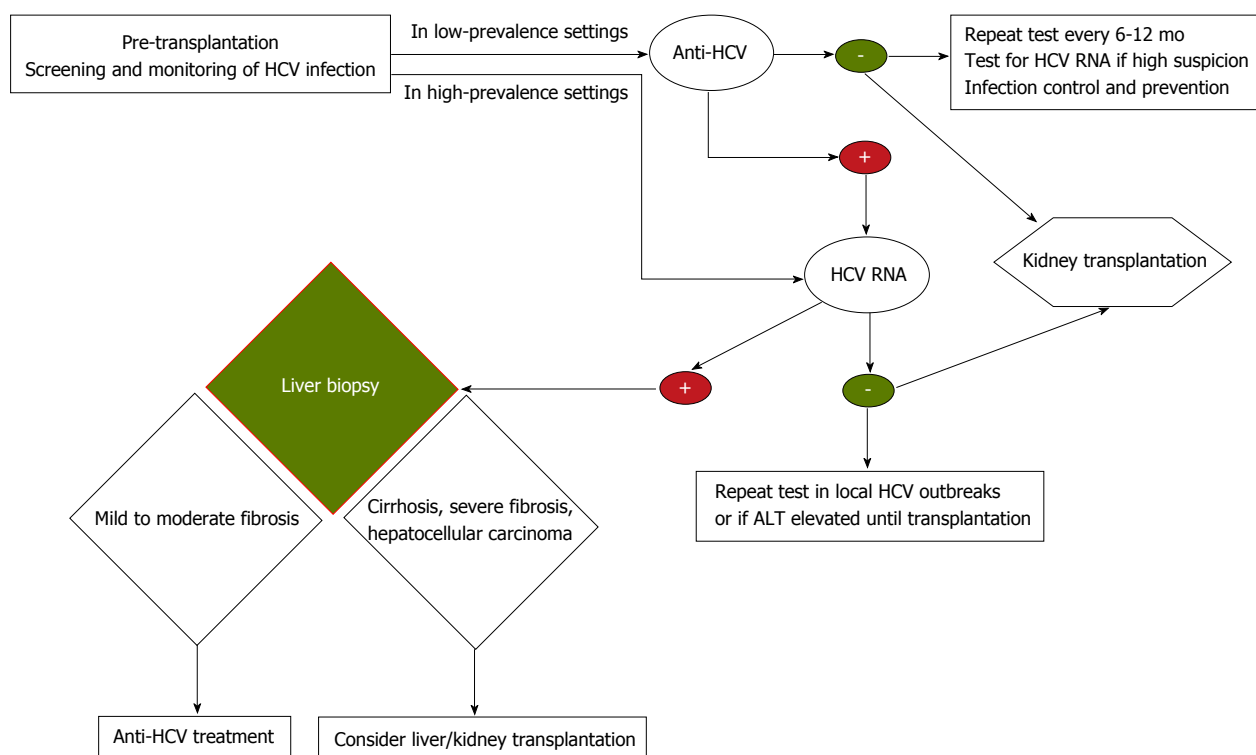


Figure 1 Decision tree for follow-up of hepatitis C virus-positive end-stage renal disease patients. HCV: Hepatitis C virus; ALT: Alanine aminotransferase.

assessing liver fibrosis in ESRD patients with HCV infection. Two of these are the aspartate aminotransferase to-platelet ratio index (APRI) and transient elastography (TE) which is performed with a Fibroscan<sup>®</sup> machine. Studies have demonstrated that APRI and TE are effective for evaluating hepatic fibrosis in HD patients with chronic HCV infection, but both methods have some limitations<sup>[37,38]</sup>. The predictive values and cut-off values for these methods as optimized for the healthy population may not be valid for ESRD patients<sup>[39]</sup>. As well, the HD procedure and the presence of uremic toxins may alter blood levels of apolipoprotein A1 and  $\alpha$ -2 macroglobulin, which can influence Fibroscan<sup>®</sup> results<sup>[37]</sup>. An APRI score cannot precisely predict the histological severity of liver disease, particularly the intermediate fibrosis stage<sup>[38]</sup>.

## NATURAL COURSE OF HCV IN ESRD PATIENTS

In patients with ESRD, chronic HCV infection usually takes an insidious clinical course. Early diagnosis and identification of individuals at greater risk for fibrosis progression should be the clinician’s main concern. Evidence clearly indicates that ESRD patients who undergo KT have more favorable results than those who do not, and that this also applies for ESRD patients with HCV infection. Every ESRD patient should be evaluated as a candidate for KT as soon as possible after diagnosis. This is important because during the interval between diagnosis and transplantation there is increased mortality

risk due to higher incidence of hepatic and non-hepatic complications. It is essential that each dialysis center carefully follows every HCV-infected ESRD patient to determine viral load, do HCV genotyping, assess the extent of hepatic fibrosis, and establish optimal treatment strategies. A decision tree for the follow-up process is shown in Figure 1. Treating HCV infection prior to KT helps to prevent post-transplantation complications and reduce mortality<sup>[3,39-42]</sup>.

There is general agreement that ESRD patients with decompensated cirrhosis and portal hypertension should be removed from the KT list and referred to the liver transplant team to be considered for combined liver-KT<sup>[43]</sup>.

It is also generally accepted that every HCV-positive ESRD patient who is being evaluated for KT should undergo a liver biopsy to assess the stage of liver disease, unless there is clear radiological or clinical evidence of portal hypertension or decompensated cirrhosis<sup>[35]</sup>. Patients with Metavir fibrosis score  $\leq 3$  on histologic examination should be considered for antiviral treatment. Patients with successful sustained viral response (SVR) are definite candidates for KT, and those on the waiting list should be tested at least annually to confirm the durability of the SVR prior to transplantation<sup>[35,41,44]</sup>. Those who have ready living-related donors could be referred for KT immediately. There is some largely anecdotal evidence that inducing an SVR prior to KT reduces the risk of post-transplantation complications. For patients who have attained SVR, some authors consider the probability of HCV reactivation to be extremely low, however, this is controversial, especially when aggressive

immunosuppression is administered<sup>[45]</sup>.

The growing number of ESRD patients with HCV-related compensated cirrhosis is a major problem. In this group, treatment is a dilemma because interferon and ribavirin carry potential risk of decompensation and serious adverse effects<sup>[3,45]</sup>. Some authors consider these patients "too healthy" for liver transplantation, and yet their limited liver reserve, poor nutritional status, and increased susceptibility to infections puts these individuals at risk for increased perioperative morbidity and mortality if they undergo KT<sup>[44]</sup>. These patients require comprehensive and detailed evaluation. Presence of portal hypertension should be carefully evaluated to decide whether KT alone or combined kidney and liver transplantation is appropriate<sup>[42,43]</sup>. It is recommended that patients with wedge hepatic vein pressure > 10 mmHg may be listed for combined kidney and liver transplantation<sup>[43]</sup>. Some transplantation centers use different criteria to make this decision, such as platelet count or presence of varices on endoscopy<sup>[44]</sup>. Making the correct treatment decision in these cases in this challenging. To improve decision-making in future, transplant centers need to report incremental experiences and long-term post-transplantation observations.

The other problematic patient group with respect to treatment decisions is ESRD patients with HCV who do not respond to antiviral treatment or who have been assessed as ineligible for antiviral treatment. As HCV replication progresses, there is greater risk of accelerated liver disease, including hepatic failure and hepatocellular carcinoma<sup>[46]</sup>. KT is not contraindicated for these individuals, but each such candidate must be informed of all difficulties (*i.e.*, those related to progression of HCV and restricted antiviral treatment) after transplantation<sup>[47]</sup>. It should also be kept in mind that extending waiting time for KT will likely result in poorer liver status for these individuals<sup>[46,47]</sup>. However, any ESRD patient with HCV who remains viremic while on a KT waiting list should be placed on hold status. These patients should be evaluated carefully and frequently to assess HCV disease status and their suitability for KT as time on the waiting list extended<sup>[44]</sup>.

### **HCV infection after KT**

The natural history of HCV infection after non-liver solid organ transplantation is still not fully understood. One study revealed that HCV-positive kidney transplant recipients had lower survival than HCV-negative patients<sup>[42]</sup>. As noted previously, KT is associated with better long-term survival for ESRD patients, even those diagnosed with HCV infection. In other words, anti-HCV positivity must not preclude HD patients from KT<sup>[48]</sup>.

### **After KT: Progression and treatment of HCV-related liver disease**

Patients with HCV infection who undergo KT can experience progression of liver disease after the operation. This has been identified as the fourth most frequent cause of mortality (reported range, 8% to 28%) in long-

term survivors of KT. Increased risk of cardiovascular disease, post-transplantation diabetes mellitus, and sepsis are considered the primary causes of death after KT<sup>[49]</sup>.

A patient's HCV viral load will increase in the setting of immunosuppression, which usually develops within the first months after KT<sup>[50]</sup>, but there is no evidence that progression of liver disease is correlated with HCV RNA load.

Kamar *et al*<sup>[47]</sup> investigated natural course of HCV-related liver fibrosis after KT. They observed that liver biopsy samples from HCV-positive patients after KT showed progression of fibrosis in 21 patients, stable phase in 21 patients, and regression of fibrosis in 10 patients. The risk factor most strongly associated with progression of hepatic fibrosis was severity of liver disease prior to KT<sup>[47]</sup>.

In HD patients with HCV who undergo KT, antiviral treatment is mandatory after renal transplantation only if the individual develops advanced fibrosis or severe cholestatic hepatitis. Both these conditions are associated with high mortality, and antiviral therapy can be life-saving<sup>[46,51]</sup>. For such patients, the decision regarding when to provide antiviral therapy should be made based on a risk-benefit assessment for each individual case<sup>[51]</sup>. The main concern about interferon (IFN) treatment is that it can trigger acute graft rejection<sup>[45,46]</sup>. The optimal approach for antiviral treatment of HCV after KT is unclear. A recent meta-analysis by Fabrizi *et al*<sup>[52]</sup> evaluated 12 clinical trials. In three of these, a combination of IFN and ribavirin was used, and the estimated rates of SVR and dropout were 18% (95%CI: 7.0%-29%) and 35% (95%CI: 20%-50%), respectively. The most frequent reason for discontinuing the combination treatment was graft dysfunction (71.7%). There is no evidence that the IFN-ribavirin combination is superior to IFN monotherapy<sup>[52]</sup>. Overall, Fabrizi *et al*<sup>[52]</sup> agree that treating these patients with anti-viral therapy before KT is safer and more effective than administering this treatment post-transplantation.

The risk for acute rejection in HCV-infected patients is higher during the first year after KT. In cases where anti-viral therapy is necessary after KT, some authors recommend waiting at least 1 year after the surgery to initiate this treatment<sup>[51]</sup>. In contrast, other research has shown that anti-viral treatment may be more effective during the first year after transplantation if the patient has stable renal function and no acute rejection occurs<sup>[53]</sup>.

Renal transplant recipients with HCV who have stable renal and liver function should be carefully monitored, as should those receiving anti-viral therapy. In all cases liver function tests should be done every 3 mo and viral load should be measured every 6 mo. Liver biopsy should be repeated every 3 years<sup>[54]</sup>.

### **After KT: Immunosuppression in patients with HCV-related liver disease**

In patients with HCV who undergo KT, immunosuppressive therapy is required to prevent rejection of

the renal graft, but this may cause a more rapid and aggressive course of HCV infection<sup>[55]</sup>. In addition to the severity and duration of HCV infection, at the time of KT, the choice of immunosuppressive drug combination and doses can significantly affect the course of HCV infection after KT. There is still controversy regarding what constitutes the most appropriate immunosuppressive combination.

Induction immunosuppressive therapies for kidney transplant recipients typically contain T-cell-depleting antibodies (OKT3, anti-thymocyte globulin). Induction therapies with non-depleting antibodies (*i.e.*, antibodies that block interleukin-2) have also been debated. There are conflicting reported outcomes regarding the hazardous or beneficial effects of these induction immunosuppressive drugs on the course of HCV infection and on survival of the renal graft. Earlier studies suggested that OKT3 was not a good choice for induction<sup>[56]</sup>, whereas a recent report by Roth *et al.*<sup>[21]</sup> indicated that patients who received OKT3 had better liver fibrosis scores than those who received daclizumab (an agent that binds the interleukin-2 receptors of T-cells). At minimum, HCV-infected patients who have undergone KT should receive a short course of induction therapy.

Glucocorticosteroids are given in wide range of doses to prevent rejection after KT. This treatment is associated with increased HCV replication<sup>[55]</sup>; however, Luan *et al.*<sup>[57]</sup> demonstrated no significant difference in mortality between patients who received steroids and those who did not. Akalin *et al.*<sup>[58]</sup> pointed out that rapid discontinuation of steroid treatment was not associated with worse outcome in HCV-positive renal transplant recipients.

Cyclosporin might inhibit HCV replication through mediating a blockage of interaction between cyclophilins and non-structural protein 5B (HCV-RNA polymerase)<sup>[59,60]</sup>. Kahraman *et al.*<sup>[61]</sup> investigated kidney recipients with HCV, and observed no significant differences between a group that received tacrolimus and a group that received cyclosporin with respect to viral replication and development of hepatic fibrosis.

Mycophenolate mofetil is known to have anti-viral effects in HCV patients, and acts by inducing the expression of anti-viral IFN-related genes<sup>[59,62]</sup>. In, there is no evidence of a specific destructive effect on either the renal graft or the HCV infection<sup>[55]</sup>.

There are scarce data on the influence of sirolimus and everolimus [both inhibitors of the mammalian target of rapamycin (mTOR)] in renal transplant recipients with HCV. Luan *et al.*<sup>[57]</sup> found that mTOR inhibitors were associated with 13% increased risk of mortality in this patient group. These drugs are not yet recommended as standard regimen for renal transplant recipients with HCV<sup>[55]</sup>.

#### **After KT: Infections**

Several studies have confirmed that HCV-positive kidney recipients are at increased risk for infections of the central

nervous system, respiratory system, urinary tract and bloodstream<sup>[41,63]</sup>. Research has identified a significant relationship between development of tuberculosis and presence of HCV infection in renal transplant recipients<sup>[64]</sup>, but it is not clear why HCV-positive recipients are more susceptible to this infection. Immunosuppression and diabetes are two possible explanations<sup>[63]</sup>.

#### **After KT: HCV-related glomerular disease**

HCV infection has been directly linked to glomerular disease in both native and transplanted kidneys<sup>[65]</sup>. The most common renal diseases associated with HCV infection are membranoproliferative glomerulonephritis with or without cryoglobulinemia and membranous glomerulonephritis<sup>[66]</sup>. Meyers *et al.*<sup>[65]</sup> hypothesized that these relationships are explained by increased HCV viral load and decreased immunoglobulin synthesis in the setting of immunosuppression, and an imbalance of antigen and antibody complex status and deposition of these complexes in the allograft. Kamar *et al.*<sup>[67]</sup> proposed that these diseases were explained by higher cytokine production rather than direct cytotoxic effects of HCV on kidney cells.

#### **After KT: HCV-related new-onset diabetes mellitus**

HCV-related new-onset diabetes after KT in patients with chronic HCV is an interesting and relatively frequent complication<sup>[35]</sup>. Reported prevalences of this in HCV-positive and HCV-negative kidney transplant recipients are 39.4% and 9.8% respectively<sup>[68]</sup>. Unfortunately, it has been shown that new onset of diabetes after KT impairs graft function<sup>[69]</sup>. The mechanisms proposed for HCV-related diabetes mellitus include increased insulin resistance, direct cytopathic action of HCV on beta cells, and side effects of immunosuppressive drugs<sup>[70,71]</sup>.

#### **After KT: HCV-related extrahepatic neoplasia**

The role of HCV in the pathogenesis of post-transplantation hematologic malignancies is obvious<sup>[72]</sup>. Post-transplant lymphoproliferative disorder was found to be significantly more frequent in HCV-positive kidney recipients than in HCV-negative kidney recipients<sup>[73]</sup>.

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## **TREATMENT OF HCV INFECTION IN PATIENTS WITH ESRD**

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Carefully treating HCV and achieving SVR prior to KT should be primary goals to reduce the likelihood of HCV-related complications in the liver and other organs/systems<sup>[74]</sup>. Another reason it is important to attain SVR before KT relates to the concern that anti-viral therapy administered post-transplantation is associated with high risk of graft rejection<sup>[75]</sup>.

The document entitled Improving Global Outcomes recommended that HCV-infected HD patients awaiting KT should be treated for HCV, and that attending clinicians should decide whether to treat other HCV-infected patients (*i.e.*, those not on the KT waiting list)

on case-by-case basis. However, HD patients with HCV infection rarely receive antiviral therapy<sup>[76]</sup>.

### **Monotherapy with standard interferon or pegylated interferon**

Several forms of IFN are available for therapeutic use, including  $\alpha$ -2a,  $\alpha$ -2b,  $\alpha$ -n1. In ESRD patients with HCV, the recommended administration of IFN ranges from 1-6 mU as a/daily dose or up to three times weekly. A long-acting IFN  $\alpha$ , namely pegylated IFN (pegIFN), has been used safely and effectively for more than a decade. Peg IFN  $\alpha$ -2a administered at 135  $\mu$ g weekly and peg IFN  $\alpha$ -2b administered at 0.5-1  $\mu$ g/kg are currently approved for HCV treatment and are administered weekly in stage 3-5 ESRD. Treatment duration is 24 wk for HCV genotypes 2 or -3 and 48 wk for HCV genotypes 1-4<sup>[77,78]</sup>.

Three recently published meta-analyses have indicated that SVR, side effects and withdrawal rates in patients with ESRD vary according to treatment with IFN and pegIFN.

The meta-analysis by Fabrizi *et al.*<sup>[79]</sup> evaluated results from 645 patients the overall SVR rate was 40%; in the subset with HCV genotype 1, the SVR rate was 33% and dropout rates were 19% in the group that received IFN and 27% in the group that received pegIFN. A typical flu-like syndrome was the most common side effect. This occurred in 41% of patients and required withdrawal of anti-viral treatment in 11%. However, the meta-analysis by Fabrizi *et al.*<sup>[79]</sup> was criticized because the studies examined were somewhat heterogeneous with regard to viral response and dropout rates.

A meta-analysis by Gordon *et al.*<sup>[80]</sup> in 2008, involved 546 chronic HD patients with HCV infection who were either treated with IFN or pegIFN, with or without ribavirin. Only 49 individuals received pegIFN and ribavirin. The overall SVR rates were 41% for the IFN group (95%CI: 33%-49%) and 37% for the pegIFN group (95%CI: 9%-77%). The frequencies of treatment discontinuation were 26% for the IFN group (95%CI: 20%-34%) and 28% for the pegIFN group (95%CI: 12%-53%). The main side effects were fatigue/weakness and loss of appetite. The authors also found that higher dose of IFN, lower HCV RNA load prior to treatment, early stage of hepatic fibrosis, and HCV genotype other than genotype 1 were associated with higher SVR rates<sup>[80]</sup>.

A more recent meta-analysis evaluated data from 770 HD patients with chronic HCV infection, 491 of whom received IFN- $\alpha$ 2a or IFN- $\alpha$ 2b and 279 of whom received pegIFN- $\alpha$ 2a or PegIFN- $\alpha$ 2b. The corresponding SVR rates for these two groups were 39.1% (95%CI: 32.1%-46.1%) and 39.3% (95%CI: 26.5%-52.1%), and the corresponding dropout rates were 22.6% (95%CI: 10.4%-34.8%) and 29.7% (95%CI: 21.7%-37.7%). Age younger than 40 years was significantly associated with SVR (OR = 2.17; 95%CI: 1.03-4.50)<sup>[81]</sup>.

Although the above three meta-analyses suggest that conventional IFN treatment and pegIFN therapy

have similar efficacy and safety, many studies have shown that pegIFN is superior<sup>[27]</sup>. For example, one study revealed that patients with renal dysfunction who were treated with pegIFN had a higher HCV eradication rate than HCV patients with normal kidney function who received this treatment. This can be attributed to decreased renal clearance of pegIFN in the setting of ESRD. In practice once weekly dosing of pegIFN is more convenient for the patients with renal dysfunction<sup>[82]</sup>.

### **Combination therapies: Interferon or pegIFN with ribavirin**

The combination of pegIFN and ribavirin is considered the gold standard therapy for patients with chronic HCV who have normal renal function<sup>[77]</sup>. Some physicians are reluctant to use ribavirin in patients with ESRD or in those who are on HD due to fear of hemolytic anemia which can be exacerbated in the presence of kidney dysfunction. Because ribavirin is filtered by the kidneys, its clearance is impaired in patients with ESRD, and this agent is not removed by dialysis. Despite the fact that ribavirin is contraindicated in the setting of renal failure, this drug can be used at markedly reduced daily doses and with careful monitoring for anemia. Patients can be started on a low dose of ribavirin, and doses can be increased gradually as long as side effects are manageable<sup>[82-84]</sup>.

Only a few reports support the combined use of pegIFN and ribavirin in ESRD patients or patients on HD (Table 1). Rendina *et al.*<sup>[88]</sup> published the largest series to date on the combined use of pegIFN  $\alpha$ -2a (135  $\mu$ g/wk) plus ribavirin (200 mg daily to every other day) for 48 wk in 35 HD patients. They observed an SVR rate of 97% (34 of the/35 patients) and a dropout rate of 14%. Only one patient developed severe anemia and had to be weaned off treatment.

The dose of ribavirin should be adjusted based on target plasma level which has been identified as 10-15  $\mu$ mol/L in patients with normal kidney function. For patients with ESRD, the average dose of ribavirin can be 200 mg daily, but some individuals can only tolerate 200 mg every other day<sup>[46]</sup>. Assays for monitoring plasma ribavirin levels are not routinely available. Even when therapeutic ribavirin levels are maintained the potential for anemia in HD patients cannot be ruled out. Recombinant human erythropoietin or blood transfusions can be while maintaining the desired ribavirin dosage, for these patients, as these measures can correct anemia and improve quality of life during treatment<sup>[83]</sup>.

### **Direct-acting anti-viral agents**

Direct-acting anti-viral agents (DAA) have yielded exciting results in ESRD patients. When combined with IFN and ribavirin, DAA increase SVR rates in patients with intact kidney function. However, anemia is an important potential side effect of DAA even in patients with normal glomerular filtration rate. Further information and experience are needed with respect to using DAA-based therapy in patients with ESRD<sup>[89]</sup>. More aggressive

**Table 1** Results from trials: Interferon-ribavirin combined treatments in patients with end-stage renal disease and hepatitis C virus infection

| Ref.                                   | Year | No. of patients | Proportion with HCV genotype 1 (%) | Treatment   | SVR (%)  | Dropout (%) |
|--|------|-----------------|------------------------------------|---|----------|-------------|
| Tan <i>et al</i> <sup>[85]</sup>       | 2001 | 5               | NA                                 | IFN-3.0 MU/d to 3 times/wk + RBV 200 mg/d, 3 times/wk for 40 wk                 | NA       | 40          |
| Mousa <i>et al</i> <sup>[86]</sup>     | 2004 | 20              | 60-66                              | IFN-3.0 MU/d to 3 times/wk + RBV 200 mg/d, 3 times/wk<br>For 24 wk<br>For 48 wk | 66<br>55 | 0<br>0      |
| Bruchfeld <i>et al</i> <sup>[87]</sup> | 2006 | 6               | 66                                 | PegIFN - 50 µg/wk + RBV 200-400 mg/d for 24-48 wk (depending on genotype)       | 50       | 50          |
| Rendina <i>et al</i> <sup>[88]</sup>   | 2007 | 35              | 45.7                               | PegIFN-α2a 135 µg/wk + RBV 200 mg/d for 24-48 wk (depending on genotype)        | 97       | 15          |

IFN: Interferon; NA: Not available; PegIFN: Pegylated IFN; RBV: Ribavirin; SVR: Sustained virological response; HCV: Hepatitis C virus.

therapy maybe considered for HD patients who are eligible for KT, as HCV eradication prior to transplantation can improve outcomes<sup>[90]</sup>.

Two new HCV drugs were approved in 2011: telaprevir and boceprevir. Both these are first-wave, first-generation NS3-4A protease inhibitors. Two other drug were approved in 2013/2014: simeprevir, a second-wave, first-generation NS3-4A protease inhibitor, and sofosbuvir, a nucleotide analogue inhibitor of viral polymerase<sup>[91]</sup>.

Triple therapy for HCV infection currently may have several opportunities including a better therapeutic schedule in patients with renal failure, which apparently do not require dose adjustments to the kidney function, yet the detailed data regarding the new drugs in these patients are not available<sup>[92]</sup>.

Sofosbuvir and simeprevir are not recommended for patients with ESRD or patients who require HD. While no dose reduction is necessary when sofosbuvir or simeprevir are administered to patients mild to moderate HCV infection, a lower dose is needed when this drug is administered to patients with severe HCV infection. Renal insufficiency has no impact on the pharmacokinetic profile of asunaprevir<sup>[93]</sup>.

The development of IFN-free or IFN-sparing regimens represents a breakthrough in the history of anti-HCV treatment. It is expected that treatment scenarios for chronic HCV patients will change radically in the next few years, as safe and potent therapies become more accessible. This will simplify the management of these cases, and will open possibilities to include patient populations for which pegIFN is currently contraindicated<sup>[94]</sup>.

In conclusion, HCV infection remains a major health problem that can cause substantial liver-related morbidity and mortality in patients with ESRD. Various forms of IFN with or without ribavirin can be used to treat ESRD patients with HCV infection prior to KT; however, only approximately one-third of these patients will achieve SVR. After an HCV-infected patient has undergone KT, IFN-based treatments are generally not recommended owing to the high risk of graft rejection. Recently introduced IFN-free treatment options are promising, but data are lacking regarding their use

in HD patients with HCV infection. Well-designed prospective studies are needed to evaluate the efficacy and safety of the new IFN-free regimens in this patient group.

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