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CHAPTER

46

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Kidney Transplantation in the Hepatitis C Infected Recipient

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46.1 INTRODUCTION

s0010

Chronic hepatitis C (HCV) infection is a leading cause of chronic liver disease worldwide, with a global prevalence rate of around 3%.[1] The prevalence of HCV infection is much higher in patients with chronic renal disease compared to the general population: approximately 6% of patients with end-stage renal disease (ESRD) on chronic replacement therapy[2] are infected with HCV, between 4%–70% of patients on hemodialysis (HD), and 11%–49% of kidney transplant (KT) recipients.[3–5] p0010

In the KT population, chronic HCV infection course is accelerated compared to the general population, being associated with a significant reduction in patient and graft survival.[6–8] The unfavorable impact of HCV infection on KT survival is likely related to liver fibrosis progression induced by the use of immunosuppressive regimens, which accelerates fibrogenesis and worsens the liver damage.[9–13] Recent evidence also suggests that chronic HCV infection is an independent risk factor for acute and chronic rejection, graft glomerulopathy, posttransplant new-onset diabetes and HCV-related glomerulonephritis in KT recipients.[14–15] p0015

Patients with an active HCV infection have a reduced long-term survival, which is associated with increased morbidity and mortality as compared with patients without HCV infection, mainly as a consequence of cardiovascular disease, or secondary to infections and liver disease. However, the overall survival appears to be better in KT patients compared to those remaining on dialysis, which highlights the importance of managing HCV infection, as well as HCV-related liver disease in these patients.[16] p0020

The management of HCV infection in KT recipient presents unique challenges. The two main factors influencing the graft outcome are the use of antiviral therapy and immunosuppressive drugs. Before the introduction of the new directly acting antiviral (DAA) drugs, the possibility to treat of HCV infection with interferon-α (IFN-α) and ribavirin (RBV) was limited by the higher renal allograft rejection rates and the related drug toxicity.[17–19] Therefore, all HCV-infected KT candidates should be evaluated for potential antiviral therapy before transplantation. Viral eradication before transplant may not only lower the risk of progressive liver disease after KT, but also of HCV-associated extrahepatic complications. No consensus has yet been reached about the optimal immunosuppressive strategy to be used in HCV-positive KT recipients.[20] p0025

Combined kidney–liver transplantation is currently also considered a valid option in patients with liver cirrhosis.[21–22] Moreover, transplantation of kidneys from HCV-positive donors to HCV-positive recipients is currently considered to be a safe long-term approach and a strategy to improve the donor pool and to reduce the waiting list for transplantation.[23] p0030

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46.2 EPIDEMIOLOGY AND RISK FACTORS OF HCV INFECTION IN PATIENTS WITH CHRONIC RENAL DISEASE s0015

HCV infection is highly prevalent in patients with ESRD undergoing HD and represents the main cause of liver disease in this population, although in recent years the prevalence has been reduced by almost one third.[24–25] The prevalence varies among different regions, with a higher frequency in developing countries (approximately 75%–80%) than in developed regions (approximately 3.4%).[26–28] Despite the elimination of post-transfusion HCV transmission due to the beginning of HCV screening in the early 1990s, the incidence of HCV infection among patients on chronic treatment dialysis remains relatively high, with seroconversion rates ranging between 0.2% and 15% per year of dialysis.[29] p0035

Patients under renal hemodialysis are exposed to blood-borne pathogens due to the need for intravenous access and frequent catheter manipulations. Although prospective trials have shown a reduction in HCV transmission within dialysis units through the complete isolation of HCV patients, this practice has not been universally accepted.[30] The Kidney Disease: Improving Global Outcomes (KDIGO) panel does not recommend the use of dedicated machines, patient isolation, or a ban on reuse in HCV patients on HD. However, strict adherence to "universal precautions," careful attention to hygiene, and sterilization of machine dialysis is emphasized. While transfusion of blood product still plays a significant epidemiological role in developing countries, the majority of HCV infections in the hemodialysis setting are currently attributed to nosocomial transmission through hand-borne transmission, or to the use of concomitant medication vials, such as saline, anesthetic drugs, and unfractionated heparin.[31–33] A systematic review of 20 studies analyzing the possible transmission routes reported that the cross-contamination from supplies and surfaces, resulting from failure of local sanitary infection-control practices, seems to be the main factor for HCV transmission.[34] p0040

The risk factors for acquiring HCV infection during dialysis include the following: number of transfusions, duration of dialysis, previous transplant, number of procedures for dialysis access, type of dialysis (the incidence in HD is higher then in peritoneal dialysis), prevalence of HCV infection in dialysis unit.[35–36] Therefore, the prevalence of HCV infection in KT recipients varies widely (from 6% to 46%). In most HCV-positive KT recipients, the infection occurs before transplant, while patients are on HD, whereas only exceptionally the acquisition of HCV infection occurs through an infected donor and is infrequently acquired after KT.[37] p0045

46.3 SCREENING AND DIAGNOSIS OF HCV INFECTION IN PATIENTS WITH ESRD s0020

46.3.1 Before Kidney Transplantation s0025

Baseline screening in dialysis patients includes serological assays for antibodies to HCV (anti-HCV) and serum alanine aminotransferase (ALT) levels. Currently third- and fourth-generation anti-HCV enzyme-linked immunoassays yield very high sensitivity rates, up to 100%, in immunocompetent patients. However, the "serological window" between acute infection and the detection of specific antibodies takes an average of 8 weeks, and in immunocompromised patients, antibody production may be delayed or absent, resulting in false-negative anti-HCV. ALT levels in patients with chronic renal dysfunction have been reported to be lower than in the general population, possibly due to suppression of ALT synthesis in hepatocytes, defective release of ALT into the blood stream, or accelerated clearance in patients with chronic renal insufficiency.[38–40] p0050

For anti-HCV-negative patients, the recommendation is to monitor ALT levels monthly, and anti-HCV every 6 months.[41] Increases in ALT levels should prompt testing for HCV infection, and if anti-HCV is negative despite persistently increased ALT levels, testing for HCV-RNA should be considered and repeated, if negative. This is especially important in patients on dialytic therapy, in whom low and fluctuating viremia might happen, resulting in undetectable viremia despite the presence of the virus. p0055

For anti-HCV positive patients, HCV-RNA testing should always be performed. A positive result confirms infection, either acute (defined as the presence of HCV-RNA for <6 months) or chronic (defined as persistence of HCV-RNA >6 months). A negative result is considered as a resolved HCV infection, or a false-positive antibody test. However, isolated undetectable results of HCV-RNA should not be interpreted as absence of replication. It is recommended for all anti-HCV positive patients on HD to perform sequential HCV-RNA monitoring, by using highly sensitive detection methods, like reverse transcriptase-polymerase chain reaction (RT-PCR) or transcription-mediated amplification.[42–43] HCV-RNA PCR-based molecular diagnostics are required also to p0060

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measure the viral load and identify the HCV genotype, in order to guide management decisions and monitoring the response to antiviral therapy.

p0065 During HD, HCV-RNA level is transiently decreased and gradually returns to baseline level within 48 hours. This may be explained by several mechanisms, such as interference with PCR technique by adsorption of HCV onto the dialysis membrane, heparin use during dialysis, destruction of HCV particles by the hydraulic pressure, hepatocyte growth factor, or increased plasma IFN levels during the dialysis. Therefore, it is recommended to determine HCV-RNA level before HD to avoid the possibility of underestimation.[40,44]

p0070 "Occult HCV infection," a new entity defined by detection of HCV-RNA in peripheral blood mononuclear cells (PBMC) and/or hepatocytes in the absence of HCV-RNA in serum, has been a matter of controversy.[6] Occult infection, which is not detectable by routine diagnostic methods, may also represent a risk for nosocomial transmission of HCV infection in dialysis units, as well as an additional risk for virus reactivation and progression of liver disease after KT. However, a recent study evaluating 417 hemodialytic subjects found only one single case (<1%) of occult HCV infection in PBMC, suggesting that this condition is indeed very rare in ESRD in HD.[45]

46.3.2 After Kidney Transplantation

s0030

p0075 In most HCV-positive KT recipients the infection occurs before transplantation, while patients were on HD. Therefore, HCV-positive recipients are often already assessed for HCV infection at the time of transplant. After KT, levels of HCV-RNA rise, as a consequence of immunosuppressive therapy.[46] A percentage of KT recipients are HCV-RNA positive, but anti-HCV negative; the reason remains still unclear, but is probably due to the inability to mount an antibody response against HCV due to the immunosuppressive drugs.[47–49] There are few data to suggest when and how to screen HCV-infected KT recipients. However, given the higher level of immunosuppression early after transplantation, the KDIGO suggested that liver enzymes should be checked every month for the first 6 months of the posttransplant period, and every 3 months thereafter.[20]

p0080 HCV has also been implicated in the pathogenesis of glomerular disease in both native and transplanted kidneys. Therefore, the Hepatitis C and Transplant Guideline Working Group concluded that HCV-infected KT recipients should be tested for proteinuria every 3–6 months. As recommended for all KT recipients, patients who develop new-onset proteinuria (either urine protein/creatinine ratio >1 or 24-hour urine protein greater than 1 g on two or more occasions) should have an allograft biopsy with immunofluorescence and electron microscopy.[20]

46.4 EVALUATION OF THE HCV-RELATED LIVER DISEASE

s0035

p0085 The evaluation of the stage of liver disease in HCV-positive KT candidates and recipients is important in determining the risk for liver-related complications. The assessment of liver disease should include clinical examination, laboratory testing and ultrasound for radiological signs of cirrhosis/portal hypertension and hepatocellular carcinoma. However, ultrasound only shows moderate sensitivity in detecting liver cirrhosis,[50] and the level of transaminases may not reflect the severity of the liver disease, or may even be normal in cirrhosis.[51,52] The detection of worsening liver enzymes should prompt referral for a hepatological evaluation. Annual liver ultrasound and assay of alpha-fetoprotein levels to screen for hepatocellular carcinoma should also be considered for all HCV patients, either before or after KT. AU:1

p0090 Liver biopsy is the gold standard for assessing the degree of fibrosis in HCV-positive patients on HD, as well as in transplant recipients.[53] Studies have demonstrated that the prevalence of advanced fibrosis and cirrhosis in liver biopsies ranges from 10% up to 25% in KT candidates with HCV infection.[52] However, its use is limited by the invasive nature, poor patient acceptance, bleeding risk, especially in uremic patients, with additional risks in patients who need invasive procedure.[54] Transjugular liver biopsy is an alternative procedure for obtaining liver specimens instead of a percutaneous approach.[55] The advantage of this procedure is due to a greater safety and the possibility of the simultaneous measurement of the hepatic venous pressure gradient (HVPG), which provides relevant prognostic information in patients with compensated liver cirrhosis (a HVPG $\geq$10 mmHg indicates the presence of a clinically significant portal hypertension). However, this procedure is not widely available and frequently provides small tissue samples, which might underestimate fibrosis staging.

p0095 The need of noninvasive tests to estimate the liver fibrosis in HCV patients has become critical in recent years. Imaging tests, such as transient elastography (FibroScan; Echosens, Paris, France) or blood-based tests, such as AST-to-platelet ratio index (APRI) have shown good diagnostic performance to predict the severity of liver

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fibrosis in the ESRD population.[56–58] Results from a meta-analysis of 40 studies showed that an APRI cut-off of 1.0 had a sensitivity of 76% and a specificity of 72% for predicting cirrhosis. Similarly, an APRI cut-off of 0.7 had a sensitivity of 77% and a specificity of 72% for predicting significant hepatic fibrosis.[59] However, transient elastography shows superior diagnostic accuracy compared to APRI in HCV patients with ESRD.[60] Yet, although these methods have been shown to be reliable for the diagnosis of cirrhosis, they are less accurate than liver biopsy in discriminating different fibrosis stages.[61]

p0100 Although there is no current agreement regarding the optimal test to estimate liver fibrosis in HCV patients before and after KT, we suggest that before transplantation the liver biopsy should remain the gold standard; after transplantation, serial transient elastography measurements may be relevant for surveillance of fibrosis progression, in particular in recipients with contraindications to liver biopsy, or in those who refuse to be biopsied, though this remains to be evaluated in further prospective studies.[52] Clearly, also an interdisciplinary management by a nephrologist and a hepatologist is essential, either before or after KT. AU:2

46.5 NATURAL HISTORY OF HCV INFECTION IN PATIENT WITH END-STAGE RENAL DISEASE s0040

p0105 The natural history of HCV infection in HD patients tends to have a mild course.[62–63] Several explanations have been proposed, including the presence of an altered immunologic state and the relatively low HCV viral load commonly observed in the HD population.[38–40] In patients with ESRD, HCV infection has distinct clinical and laboratory features as compared to the general population and KT recipients; ALT levels and HCV viral loads are lower then those observed in nonuremic patients, even in the presence of significant histological damage. The prevalence of advanced liver fibrosis is lower (4%–10%) and progression to cirrhosis during HD seems to be uncommon.[64–65]

p0110 Despite this, the unfavorable impact of HCV-related liver disease on mortality in patients with ESRD has been well documented. Infected patients have a 25% increased risk of mortality on HD compared with HCV-negative subjects.[66–67] In the last decades, meta-analyses demonstrated that the presence of anti-HCV antibody in the HD population represents an independent significant risk factor for death.[68] Interestingly, in the ESRD setting, the increased mortality in HCV-positive versus HCV-negative patients is due not only to liver-related deaths, but also to cardiovascular mortality.[69]

p0115 ESRD candidates to KT with cirrhosis, particularly those with portal hypertension, may have a decreased survival and increased morbidity after KT. Therefore, patients with cirrhosis, but without significant portal hypertension, should be evaluated for isolated KT; however, in candidates with advanced fibrosis or cirrhosis, liver imaging monitoring and upper endoscopy are recommended for the screening of hepatocellular carcinoma and esophageal varices, respectively. If signs of decompensated cirrhosis occur, KT alone is contraindicated and combined liver–kidney transplantation should be considered.[21,22]

46.6 NATURAL HISTORY OF HCV INFECTION AFTER KT s0045

p0120 Several studies reported that HCV infection is associated with increased liver-related mortality and fibrosis progression in HCV-infected KT patients, with a significant reduction in patient and graft survival. This is possibly related to an accelerated progression of HCV-related liver disease, but also to an unfavorable effect of HCV infection in the challenging KT recipient setting, due to the increased risk of graft rejection and glomerulopathy, new-onset diabetes, HCV-related glomerulonephritis and posttransplant malignancy. Therefore, clinical consequences of HCV infection after KT can be classified as renal disease induced by HCV infection, and hepatic and extrahepatic complications.

46.6.1 Renal Disease Induced by HCV After KT s0050

46.6.1.1 De Novo and Recurrent Glomerulonephritis s0055

p0125 Glomerular lesions have been described in native and transplanted kidneys of patients with HCV infection.[70] After KT, new-onset or recurrence of membranoproliferative glomerulonephritis (MPGN), with or without

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cryoglobulinemia, membranous glomerulonephritis, acute or chronic transplant glomerulopathy (TG), and anticardiolipin-associated thrombotic microangiopathy have been described.[71]

p0130 MPGN is the most frequent glomerular lesion associated with chronic HCV in KT, followed by membranous glomerulonephritis. The pathogenesis of HCV-associated glomerulonephritis might be explained by an altered antibody to antigen ratio caused by the deposition of immunocomplexes that contain HCV-RNA in the kidneys of immunosuppressed recipients.[72] This results in immune complex-mediated glomerulonephritis. Notably, HCV-associated glomerulonephritis is unrelated to the severity of liver disease.

46.6.1.2 Transplant Glomerulopathy

s0060

p0135 AU:3 TG is a glomerular lesion unique to kidney graft characterized by the duplication/multilayering of the glomerular basement membrane, usually thought to be a manifestation of a chronic antibody-mediated rejection.[73] However, the histological features of TG and HCV-associated MPGN are similar; therefore, an association of HCV infection and TG was suggested.[74] One study showed that the prevalence of anti-HCV antibodies was higher in patients with (33%) than in those without TG (1.9%).[75] TG is associated with a poor allograft survival, which seems to be worse if TG is associated with HCV infection. Yet, it is unclear why only few patients with HCV infection develop this complication.

46.6.1.3 Acute Graft Rejection

s0065

p0140 The effect of HCV infection on the risk of acute rejection is controversial. Some authors observed a decreased rate of acute rejection in HCV-infected recipients,[76] which has not been confirmed in other studies.[77] The rate of acute rejection in patients with HCV infection has been reported to be around 14.5% over a 20-year period. In the AU:4 study by Forman et al., a higher incidence of antibody-mediated acute rejection was reported at univariate analysis in HCV-positive (19%) compared to HCV-negative recipients (6%), but this result was not confirmed to be independent after adjusting for confounding factors.[78] Another study based on protocol biopsies in 435 recipients obtained within the first 6 months after KT showed that subclinical acute rejection and HCV infection were independent factors of allograft loss.[79] Based on these data, the relationship between HCV infection and acute renal allograft rejection remains currently unclear.

46.6.2 Hepatic Complications After KT

s0070

p0145 HCV infection is the major cause of liver disease after KT and it is associated with increased mortality (51). Both the severity and duration of HCV infection and associated comorbidities are determinant for the clinical course. Chronic hepatitis and its possible progression toward cirrhosis are the main forms of liver disease. In addition, a rare but severe form of liver disease known as fibrosing cholestatic hepatitis (FCH), characterized by severe cholestasis and rapidly progressive liver failure, has been reported.[80–81]

p0150 The main cause of an accelerated HCV-related disease progression after transplant is the immunosuppressive regimen, which favors increased fibrogenesis.[9–13] Recent data suggested that fibrosis progression is faster if HCV infection is acquired during or after KT.[82] However, fibrosis progression in HCV-positive KT recipients has been reported to be heterogeneous: some studies found an accelerated fibrosis progression, while others suggested a stable histology after the transplant.[52,83] A possible explanation for these discordant rates of fibrosis progression may be due to the differences in immunosuppressive regimens. Immunosuppression therapy is also associated with a significant increase of HCV viral load.[28] However, a high viral load does not necessarily lead to more severe fibrosis in KT recipients,[73] except for FCH, which possibly results from direct viral hepatotoxicity due to an extremely high intracellular viral load (70). Interestingly, similarly to HD subjects, there is a very low prevalence of occult HCV infection in KT recipients.[18,19] HCV-induced cirrhosis is associated with a high risk of HCC development. HCC incidence may be higher in KT patients compared to the general population, especially in countries with a high prevalence of chronic hepatitis B and C infections.[84–86] Therefore, as in the pretransplant period, all patients with cirrhosis after transplantation should undergo HCC surveillance by liver ultrasonography every 6 months.[50]

46.6.3 Extrahepatic Complications After KT

s0075

46.6.3.1 New-Onset Diabetes After Transplantation

s0080

p0155 The relation of HCV infection to insulin resistance and diabetes mellitus in the general population is well documented. The pathogenesis of diabetes mellitus in HCV infection mainly involves the development of insulin

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resistance, due to the inhibition of the insulin regulatory pathways induced by HCV infection.[16] A meta-analysis identified that HCV-positive KT recipients have an increased risk of new-onset diabetes after transplantation (NODAT).[87] Consequently, NODAT is considered an independent risk factor for death, and may be one of the main factors responsible for the lower patient and graft survival in HCV-positive KT recipients. The association of HCV and NODAT is also influenced by traditional risk factors, such as obesity, old age, ethnicity (Hispanic or Afro-American), and a positive family history of diabetes mellitus. In HCV-positive KT recipients, NODAT usually occurs in the initial months after transplantation, when higher doses of immunosuppressive drugs are usually administered.[88] Consequently, in these recipients, the use of tacrolimus should be minimized, AU:5
and steroid-sparing immunosuppressive strategies might be preferable.

46.6.3.2 Infections s0085

The possible association of HCV-related liver disease and other infections after renal transplantation is contradictory. Several studies found a significantly increased risk for infections in HCV-positive recipients during the first 6–12 months after KT. In contrast, a recent meta-analysis reported no differences of secondary infections in HCV-positive compared to recipient HCV-negative patients after KT.[13] The latter data have been confirmed by a multicenter study, which showed no differences in the overall incidence of infections (bacterial, viral, and fungal) in HCV-recipients, except for bloodstream infections.[68] Furthermore, in a single retrospective case-control study, HCV infection was demonstrated to be an independent risk factor for posttransplant tuberculosis.[89] p0160

46.6.3.3 Extrahepatic Malignancies s0090

The association of HCV infection and posttransplant lymphoproliferative disorder and myeloma has been reported.[90–92] A recent study described that hematological malignancies are the third most common cause of death in patients infected with HCV, supporting the view that HCV infection could have a role in their pathogenesis.[93] A direct effect of HCV infection on cancerogenesis of lymphoid cells has also been demonstrated and reports of lymphoma regression after antiviral treatment further support this potential association.[94] However, the causal relationship remains unclear. Strict surveillance for malignancy in HCV-infected recipients is therefore recommended.[20] p0165

46.7 IMMUNOSUPPRESSION IN HCV-POSITIVE KT RECIPIENTS s0095

Immunosuppression in HCV-positive KT recipients is a challenge. The choice of the initial and maintenance immunosuppressive regimen may in fact be crucial in order to avoid a raise in HCV viral load and an acceleration of HCV-induced progression of liver fibrosis. A further crucial point is the treatment of acute rejection episodes with steroids, which is well known to favor HCV replication. Therefore, the addition of any further immunosuppressive drug always needs to be accurately evaluated, as it is mandatory to choose an immunosuppressive regimen providing an adequate control of both rejection episodes and progression of HCV-related liver damage. Unfortunately, the lack of controlled studies in this setting does not help to support, or deny, any specific immunosuppressive regimen. Therefore, the KDIGO and ERBP guidelines recommend using the conventional immunosuppressive regimens currently given for HCV-negative patients also in HCV-positive recipients.[95] p0170

In vitro studies have shown that Cyclosporine (CsA) may inhibit HCV replication, but in the clinical setting this antiviral effect remains controversial.[96–98] The United States Renal Data System (USRDS) registry reported a better graft survival in KT recipients treated with mycophenolate mofetil (MMF), than in those with other immunosuppressive therapy.[97] Interestingly, the association of MMF and increasing graft survival in HCV-positive recipients has been reported also in the liver transplant setting. Manzia et al., e.g., reported that MMF monotherapy was associated with a favorable effect on biopsy-proven hepatic fibrosis progression in HCV liver transplant recipients, compared with monotherapy with calcineurin inhibitors (CNIs).[99] p0175

Recently, the mammalian target of rapamycin (mTOR) inhibitors, a new class of potent immunosuppressive drugs, has been ordinarily introduced in immunosuppression regimens after KT. Beyond their immunosuppressive action, both Sirolimus and Everolimus exert antiangiogenic, antiproliferative, and antifibrotic properties.[100–103] In addition, mTOR inhibitors have been associated with a lower incidence of viral infections. In a recent systematic review and meta-analysis it was reported that CMV prophylaxis might be promoted by the use of mTOR inhibitors.[104] Recently, Soliman et al. reported that conversion from CNI to sirolimus may suppress viral replication in HCV-positive renal transplant candidates. In a series of 25 HCV-positive KT recipients, 10 p0180

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patients were switched to sirolimus and 15 patients remained under CsA. Patient receiving sirolimus showed a slight decrease in HCV-RNA levels, with similar decreases in serum transaminases, suggesting a possible advantage of sirolimus in this setting.[105]

p0185 Despite the limited data available related to the effects of mTOR inhibitors on HCV infection and disease progression in KT recipients, more data have been reported on the use of these drugs in HCV-positive liver transplant recipients. A recent retrospective study, analyzing 190 patients undergoing first liver transplant for HCV-related end-stage liver disease over a 15-year period, showed that 113 patients switched from CNIs-based therapy to low-dose sirolimus monotherapy had improved survival ($P < .001$) and slower progression to cirrhosis ($P = .001$).[106] Similarly, Kelly et al. observed at the multivariate analysis decreased odds of biopsy-proven hepatic fibrosis 1 year after liver transplantation in recipients who received sirolimus therapy.[107] Furthermore, in a randomized multicenter, open-label study, 43 liver transplant recipients with recurrent HCV infection were randomized to continue CNI-based immunosuppression or to switch to everolimus. After 1 year, in patients receiving everolimus, the Ishak fibrosis score decreased significantly (by a mean of −0.7), while it slightly increased in patients who continued CNIs, suggesting that conversion to everolimus might be beneficial to control disease progression.[108]

p0190 No similar data have been reported in the KT setting. In addition, the mechanisms underlying the possible favorable effect of mTOR inhibitors on the progression of HCV-related liver disease are still unclear. TGF-β1 may exert a crucial role, since it has been identified as a most potent stimulus for hepatic fibrogenesis through activation of hepatic stellate cells.[109] Of note, a recent paper reported that everolimus decreases the serum expression of fibrosis markers in liver transplant recipients by reducing TGF-β1 and hyaluronic acid, an essential component of the extracellular matrix which is mostly synthesized by hepatic stellate cells.[110] In conclusion, while larger prospective studies are definitely needed to better address the optimal use of new immunosuppressive drugs in HCV-positive KT recipients, current data suggest that mTOR inhibitors may have a greater role in the future.

46.8 CURRENT PERSPECTIVES OF TREATMENT OF HCV-INFECTED PATIENTS ON HEMODYALISIS AND IN KT RECIPIENTS WITH ANTIVIRALS

s0100

p0195 Eradication of HCV infection in patients with ESRD, as well as in KT recipients, is a long-term recognized unmet clinical need. The rationale for treating HCV before KT is that treatment may avoid not only liver-related mortality, but also HCV-specific causes of kidney graft dysfunction, as discussed above. This suggests that an effective antiviral treatment should be initiated as soon as possible, ideally in the pretransplant setting. AU:6 Unfortunately, treatment of HCV infection in patients with ESRD, or under HD replacement, with the conventional dual therapy based on peg-interferon alfa (Peg-IFN) and ribavirin has shown a limited efficacy and to be associated with significant side effects. The main limitation is that ribavirin cannot be used at adequate doses in patients with moderate/severe kidney diseases (KD) and in those with ESRD, as it is associated with severe drug-induced hemolytic anemia. As a consequence, in most cases conventional peg-IFN based treatment has been used as monotherapy, or together with very low doses of ribavirin (e.g., 200 mg/day or less). This resulted in sustained virological response (SVR) rates in the range of 20%−25% or less, except in the relatively small number of patients infected with HCV genotype 2. On the other hand, treatment with IFN-based therapies in KT recipients has always been regarded as a too risky approach, because of the fear of inducing acute rejection by IFN administration. Although the extent of this risk has never been formally evaluated, this has de facto discouraged the use of conventional antiviral therapy in KT recipients.

p0200 The recent development and availability of DAAs against HCV has brought the enormous potential to change this unfavorable scenario into a much more promising one. Beside the use of first generation DAAs, telaprevir, and boceprevir, which have rapidly been abandoned because of severe side effects and difficult treatment schedules, the advent of the single-pill second generation DAA sofosbuvir, and of other very effective second generation drugs, has dramatically increased the possibility of cure of HCV infection during the last 2 years. These AU:7 drugs, either alone or in combination, are capable of eradicating HCV infection in approximately 85%−95% of patients with normal renal function, with minor changes mainly depending on the HCV genotype and the extent of liver disease.[111]

p0205 Unfortunately, at present no formal data on the safety and efficacy have been published on the use of DAAs in patients with renal dysfunction, nor in those with ESRD, or in KT recipients. The only available information

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derives from the registration data, which have been used by the international drug agencies (Food and Drug Administration and European Medicine Agency) to allow drug licensing for commercialization. Most registration trials have been conducted in patients with eGFR >30 mL/minute, thus most drugs have been currently licensed only for the use in patients with normal renal function.

p0210 Sofosbuvir, a specific HCV NS5B mucleosidic inhibitor, which is the most currently-used drug, at a dose of 400 mg/daily, is predominantly renally excreted (>80%). It is found in urine mostly as the dephosphorylated metabolite GS-331007. Because of the predominant renal excretion and the expected high drug or metabolite exposure in the presence of severe renal impairment, sofosbuvir is not currently recommended in patients with estimated glomerular filtration rate (eGFR) <30 mL/minute. Similarly, the combination of sofosbuvir and ledispavir (a HCV NS5A inhibitor) is currently not recommended in patients with severe renal impairment (<30 mL/minute), or ESRD. However, in a preliminary phase 2b study including 40 patients infected with HCV G1 and G3 with eGFR <30 mL/minute (EKD stage 4), presented at the 2014 Annual Liver Meeting (AASLD, Boston November 2014), Gane et al. have explored the safety and the pharmacokinetics of a different schedule of sofosbuvir (200 mg QD and GS-331007). The authors found: (1) similar virologic response compared to patients with normal renal function; (2) similar blood exposure of the two drugs; (3) slightly improved eGFR during therapy; and (4) satisfactory SVR rates at 4 and 12 weeks. They concluded that sofosbuvir, 200 mg/daily, and ribavirin are relatively well tolerated in patients with severe renal impairment, with exacerbation of anemia due to ribavirin-induced hemolysis.

p0215 DAAs other than sofosbuvir show potentially safer therapeutic profiles in patients with KD. Simeprevir, a specific NS3 protease inhibitor, is highly albumin bounded in serum and hence predominantly excreted in bile, AU:8 rather than in urine. The same occurs for daclatasvir, another HCV inhibitor of NS5A. Therefore, both simeprevir and daclatasvir, although not yet formally studied in patients with severe KD, can reasonably be used in patients with eGFR <30 mL/minute, without requiring dose adjustment with respect to the conventional doses (150 mg and 60 mg/daily, respectively). Also paritaprevir (an NS3-4A protease-inhibitor), ombitasvir (a NS5A inhibitor), and dasabuvir (a nonnucleotide NS5B polymerase inhibitor) are predominantly excreted in feces, and have a minimal renal clearance. Thus, their combination could also be safely used, without dose adjustments, in patients with moderate or severe renal disease, but it remains unknown whether this widely prescribed drug combination can be used in those under HD.

p0220 Based on the available data, current guidelines of the European Association for the Study of the Liver recommend that all patients under HD, particularly those who are candidates for KT, should be considered for antiviral therapy, preferably using IFN-free schedules. Since simeprevir, daclatasvir, and the combination of ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir are mainly excreted through the biliary route, these drugs should be preferably used in patients with severe renal disease. Conversely, sofosbuvir should not be used in these patients until more data will become available. However, the optimal doses of all these drugs in patients under HD are unknown and therefore all they should be used with extreme caution and only in life-threatening conditions. Similarly, no recommendations can be currently given for the use of DAAs in KT recipients, although it is likely that it will become soon possible to cure HCV in these patients using DAAs not interfering with immunosuppressive drugs. Several studies are currently under way to test the safety and efficacy of different DAAs and their combinations in patients under HD as in KT recipients with HCV infection. Their results, expected by the end of 2015 or mid-2016, are greatly awaited. AU:9

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NON-PRINT ITEM

Abstract

Chronic hepatitis C (HCV) infection has a high incidence in patients with end-stage renal disease and affects between 11% and 49% of the kidney transplant (KT) recipients. After transplantation, HCV infection course is accelerated compared to the general population, and is associated with significant reduction in patient and graft survival. The unfavorable impact of HCV infection on KT survival is mainly related to an accelerated liver disease induced by the use of immunosuppression drugs and specific HVC-related renal disease, including graft glomerulopathy, posttransplant new-onset diabetes, glomerulonephritis, and higher risk of acute and chronic graft rejection. Therefore, the choice of adequate immunosuppression regimen and of antiviral treatment before and after transplantation both play a critical role in HCV-positive KT recipient.

Keywords: Epidemiology; extrahepatic complications; glomerulonephritis; hepatic complications after kidney transplant; screening for infection