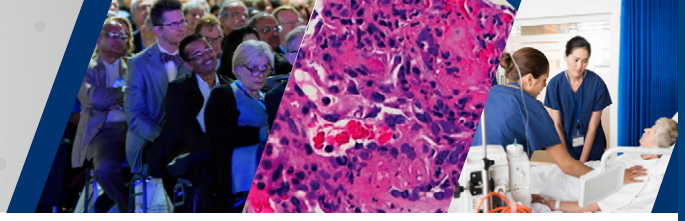

Hepatitis C Virus Infection in ESKD Patients

Marco Ladino[1,2] *and David Roth*[1]

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Introduction

Hepatitis C virus (HCV) infection represents a global health challenge with approximately 150 million people infected worldwide. The prevalence of HCV infection in patients with ESKD exceeds that of the general population and has been associated with an increase in morbidity and a higher risk of death secondary to hepatic and extrahepatic manifestations of the disease (1,2). With a prevalence of approximately 5%–10% of the United States dialysis population, it is not entirely surprising that horizontal transmission of HCV infection within clinics has occurred from breakdowns in universal precautions (1). Furthermore, data from the Dialysis Outcomes and Practice Patterns Study has provided clear evidence that the treatment of HCV among patients with ESKD has remained substantially behind that of the general population (3).

Successful mapping of the HCV genome led to the development of drugs targeting nonstructural components of the virus that are critical for viral replication. The direct acting antiviral (DAA) agents deliver sustained virologic response rates (undetectable viral load 12 weeks after completion of treatment; SVR12) that routinely exceed 90% after an 8- or 12-week course of therapy. After publication of the pivotal studies completed in the general population (1,4), trials that focused on patients with CKD and ESKD infected with HCV reproduced these excellent results with low adverse event profiles (5–8). With the availability of safe and effective treatment options for patients with kidney disease, it is important that nephrologists be familiar with the therapeutic possibilities best suited for those with ESKD infected with HCV.

We present two patients as a discussion point for the treatment of HCV infection in patients with ESKD.

Illustrative Patients

Patient One: Assessment and Evaluation of HCV Infection in a Patient with ESKD

A 65-year-old man developed ESKD from longstanding hypertension and type 2 diabetes mellitus. Screening obtained on entry to the dialysis clinic demonstrated an ELISA positive for anti-HCV antibody. Follow-up nucleic acid testing (NAT) confirmed active infection with genotype 1a and a viral load of 1.2×10^6 copies/ml. He had been previously referred to the transplant center and notification was received that he had been activated on the deceased donor waiting list. When evaluated by the hepatology service, a mild elevation of the serum transaminases was noted and there were no indications for a combined liver/kidney transplant. The average waiting time for a deceased donor kidney in our geographic region is about 5 years.

We suggest screening all patients for HCV infection at the initiation of dialysis. The Center for Disease Control (CDC) recommends screening with an ELISA that detects non-neutralizing antibody to HCV. Essentially, all patients with active infection and those who cleared the infection either spontaneously or after antiviral therapy will test positive on an ELISA. Of note, a small number of patients with ESKD who are infected with HCV may not generate an effective antibody response and will return a false negative result on ELISA testing. A positive ELISA test should be followed by NAT for HCV RNA to confirm the presence of viremia. Patients with ESKD who are on hemodialysis without evidence of infection should continue to be screened with ELISA testing every 6 months, per CDC recommendations. As the more widespread use of DAAs in dialysis clinics results in the cure of an increasing number of patients with ESKD, we believe that screening protocols that exclusively use ELISA testing will become problematic because the successfully treated patient will need to be screened for reinfection with NAT. At present, the CDC guidelines do not recognize this clinical scenario.

Chronic HCV infection is not a contraindication for kidney transplantation, with the caveat that the extent of liver injury must be determined as part of the pretransplant evaluation. In this context, liver biopsy has long been considered the gold standard; however, several noninvasive assessments of liver fibrosis are now available that have made liver biopsy far less necessary (4). At our center, initial testing for most patients is performed with the FibroScan (Echosens). Further testing is recommended for those patients whose results suggest advanced liver disease, including transjugular measurement of hepatic venous pressure gradient (to rule out portal hypertension) and liver biopsy. In consultation with our hepatologists, a decision is reached as to whether the patient is

[1]Katz Family Division of Nephrology and Hypertension, University of Miami Miller School of Medicine; and [2]Nephrology and Hypertension Section, Miami Veterans Administration Hospital, Miami, Florida

Correspondence: Dr. David Roth, University of Miami Miller School of Medicine, Room 813, 1120 NW 14th Street, Miami, FL 33136. Email: d.roth@miami.edu

suitable for kidney-only transplant or should be referred to the liver transplant team for consideration of combined liver/kidney transplantation.

Patients having a living donor are usually treated with DAAs before transplant to achieve a sustained virologic response (4). At our center, patients infected with HCV who will receive a deceased donor kidney have the option of signing informed consent to receive a kidney from an anti–HCV-positive donor. Antiviral treatment is then initiated in the early period post-transplant (4). In our experience as well as others, the waiting time for a kidney from a positive donor is substantially less than that for a kidney from an HCV-negative donor, with the advantage that dialysis vintage is considerably decreased (9,10).

Patient One Revisited

Our patient signed a consent to accept a kidney from an HCV-positive donor. He was on the waiting list for 6 months before receiving a kidney from a Public Health Service high-risk HCV NAT-positive deceased organ donor. He received induction therapy with thymoglobulin and basiliximab (Simulect) and maintenance immunosuppression with tacrolimus and mycophenolic acid. Referral for antiviral therapy followed about 2 months later, at which time he had an eGFR of 55 ml/min.

Several studies have demonstrated the safety and efficacy of treating HCV infection with DAAs in the post-transplant setting (9,10). In this context, we initiated DAA therapy with ledipasvir/sofosbuvir (Harvoni) for 12 weeks and achieved SVR12. In our experience, tacrolimus levels must be carefully monitored after beginning DAA therapy because many patients will require dosing adjustments to maintain therapeutic levels (4,10). In fact, this patient needed an approximate 25% increase in his tacrolimus dose. He tolerated the regimen well, with normalization of serum transaminases. He continues with excellent allograft function and no evidence of HCV infection at 2 years post-transplant.

Patient Two: How to Treat HCV in Patients with ESKD

A 70-year-old man developed ESKD from autosomal dominant polycystic kidney disease. He has a long history of genotype 1a HCV infection with a viral load of 3.0×10^6 copies/ml. He received a diagnosis of non-Hodgkin B cell lymphoma several months previously. He was not deemed to be a good candidate for kidney transplantation at this time.

Treatment Options for HCV Infection in Patients with ESKD

In our view, all patients with ESKD and HCV infection are candidates for treatment with DAAs unless their comorbidities are such that their estimated life expectancy is <1 year. However, determining the optimal time to treat is an important decision and requires a multidisciplinary approach including the nephrologist, hepatologist, and the transplant center. Data from several studies illustrate the safety and efficacy of HCV treatment in patients with CKD and ESKD. Grazoprevir plus elbasvir was studied in a randomized, prospective phase 3 study of treatment-naive and treatment-experienced patients with HCV genotype 1 infection and stage 4–5 CKD/ESKD (C-SURFER). The SVR12 was 94% and minimal adverse events were reported (7). In a nonrandomized, observational study, the pan-genotypic combination of glecaprevir and pibrentasvir was evaluated in patients with advanced CKD/ESKD (EXPEDITION 4). An SVR12 of 98% was achieved with minimal adverse events (8). The HCV-TARGET (Hepatitis C therapeutic registry and research network) is a real-world outcome study of sofosbuvir-based regimens (5). Importantly, there is an increased area under the curve for sofosbuvir and its major metabolite (GS-331007) in patients with advanced CKD because kidney excretion is the major method for clearance. In HCV-TARGET, patients with eGFR<30 ml/min at initiation of therapy had higher rates of anemia and deterioration of kidney function, perhaps because of the higher drug exposure. Now that there are several safe and effective DAA options available to offer our patients with ESKD and HCV infection, we would recommend against the use of sofosbuvir in this setting in preference to either grazoprevir/elbasvir or glecaprevir and pibrentasvir.

Patient Two Revisited

In the context of his lymphoma diagnosis and active HCV infection, our patient received grazoprevir/elbasvir for 12 weeks with no significant side effects, and achieved SVR12. His lymphoma was successfully treated with appropriate chemotherapy and he remains stable on dialysis and in remission for his lymphoma. He is not considered a transplant candidate at this time because of his recent malignancy.

The availability of DAAs that are safe and effective for use in patients with ESKD has had a major effect on the treatment of HCV in the dialysis clinic. We strongly recommend that nephrologists become familiarized with these treatment options. Moreover, as we are often the *de facto* primary care physician for our patients with ESKD, we should take an active role in determining the optimal time to initiate DAA treatment—a decision that hinges on both the transplant candidacy of the patient and whether the local center transplants kidneys from HCV-infected donors. Nephrologists have access to all of this information and are in the best position to make these important decisions.

Disclosures

M.L. declares no competing interests. D.R. is a consultant and is on scientific advisory boards for Merck Co. and Abbvie.

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