Hepatitis C Viral Infection in Patients with Chronic Kidney Disease

Andres F. Carrion, M.D.^{*,‡} and Paul Martin, M.D.[†]

Hepatitis C virus (HCV) infection persists as a frequent cause of chronic liver disease in individuals with chronic kidney disease (CKD) who are receiving long-term renal replacement therapy (RRT). The seroprevalence of anti-HCV antibodies is approximately 5-fold higher in patients undergoing chronic hemodialysis in the United States versus the general US population (7.8% versus 1.6%).^{1,2} Although HCV infection is an established cause of glomerulonephritis (typically mediated by cryoglobulins), it appears to be an uncommon cause of CKD requiring RRT and/or renal transplantation.^{3,4} Many cases of HCV infection in this population reflect the acquisition of an infection during dialysis. The risk of HCV infection varies with the type of RRT, with patients undergoing maintenance hemodialysis having the highest prevalence of hepatitis C.⁵ Importantly, the risk of the nosocomial transmission of HCV is proportional to the time spent on hemodialysis and to the prevalence of the infection within individual hemodialysis units.^{5–8} Data from Asian-Pacific centers have revealed a significantly higher seroprevalence of anti-HCV antibodies in individuals undergoing hemodialysis versus individuals undergoing peritoneal dialysis (7.9% ± 5.5% versus 3.0% ± 2.0%).⁹ Similarly, the incidence of HCV infection (based on seroconversion rates) is 3-fold higher in individuals undergoing hemodialysis versus individuals undergoing peritoneal dialysis.⁹ Mortality rates, however, were comparable in HCV-infected individuals undergoing hemodialysis and HCV-infected individuals undergoing peritoneal dialysis in the Asian-Pacific region, and this suggests that the mode of dialysis does not affect mortality once patients are infected with HCV.^{9,10}

Chronic HCV infection is associated with a 57% higher risk of death in patients with CKD undergoing hemodialysis

versus HCV-negative hemodialysis controls.¹¹ The increased mortality reflects not only hepatic dysfunction but also an increased prevalence of cardiovascular diseases and anemia, coinfection with hepatitis B virus and/or human immunodeficiency virus, and essential mixed (type II) cryoglobulinemia.^{11–13} HCV infections also adversely affect patient and graft survival after renal transplantation. In a meta-analysis, HCV-infected transplant recipients had relative risks of death and graft loss after renal transplantation of 1.79 and 1.57, respectively, in comparison with noninfected recipients.¹⁴ This increased post-renal transplant mortality in HCV-infected individuals is predominantly related to the higher incidence of liver cirrhosis and hepatocellular carcinoma; however, other factors implicated in inferior patient and graft survival include the recurrence of the original renal disease in the renal allograft, *de novo* allograft nephropathy, the development of posttransplant diabetes mellitus, and a higher incidence of sepsis.^{15–18} Therefore, there are cogent reasons for offering anti-HCV therapy to individuals with CKD and HCV infection and particularly to candidates for renal transplantation (a subgroup with potentially good long-term survival).^{19,20} In renal transplant candidates who achieve a sustained virological response (SVR), there is a decreased incidence of graft glomerulonephritis and post-transplant diabetes mellitus.^{19,21}

Treatment of HCV in Patients With CKD

Treatment of HCV in Patients With CKD Not Requiring RRT. The 2009 guidelines from the American Association for the Study of Liver Diseases (AASLD) endorse combination therapy with pegylated interferon (PEG-IFN) and

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CKD, chronic kidney disease; DAA, direct-acting antiviral; ESA, erythropoietin-stimulating agent; HCV, hepatitis C virus; IFN, interferon; PEG-IFN, pegylated interferon; RRT, renal replacement therapy; SVR, sustained virological response.

From the ^{*}Department of Medicine and [†]Division of Hepatology, University of Miami Miller School of Medicine, Miami, FL; and [‡]Miami VA Medical Center, Miami, FL.

Potential conflict of interest: Nothing to report.

View this article online at wileyonlinelibrary.com

© 2012 by the American Association for the Study of Liver Diseases

doi: 10.1002/cld.55

TABLE 1: Therapeutic Regimens for HCV in Individuals With Different Stages of CKD

CKD Stage	Creatinine Clearance (mL/minute/1.73 m ²)	Anti-HCV Therapy
1	≥90	PEG-IFN and ribavirin with or without DAA agents (for HCV genotype 1 infections)
2	60-90	
3	30-59	PEG-IFNα2b (1 lg/kg) or PEG-IFNα2a (135 lg) subcutaneously once a week plus ribavirin (200-800 mg/day divided into 2 doses)
4	15-29	
5: no dialysis	<15	
5: dialysis	<15	Standard IFNα2a or IFNα2b (3,000,000 U subcutaneously 3 times per week), PEG-IFNα2a (135 μg/week subcutaneously), or PEG-IFNα2b (1 μg/kg/week) with or without ribavirin (very low dose)

This table was adapted with permission from *Hepatology*.²²

ribavirin at standard doses for individuals with renal dysfunction if the creatinine clearance is ≥ 60 mL/minute/1.73 m² (CKD stages 1 and 2).²² The appropriate antiviral regimen for patients with more advanced CKD (stages 3-5) remains unsettled. Interferon (IFN) clearance is predominantly renal; therefore, individuals with more advanced CKD have a higher frequency of side effects than individuals with normal renal function.²³ IFN-related side effects in patients with more advanced stages of CKD include neurological, gastrointestinal, and influenza-like symptoms, which translate into lower tolerability and higher dropout rates.^{23,24} Ribavirin is generally not recommended for individuals with a creatinine clearance < 50 mL/minute/1.73 m² because it is also predominantly renally excreted.²⁵ Ribavirin-induced hemolytic anemia is its major toxicity and an important concern in individuals with CKD because of the high prevalence of baseline anemia.²⁶ The antiviral activity of ribavirin is dose-dependent, and dose reductions, which are often required in individuals with advanced stages of CKD, result in lower SVR rates.^{27,28}

The 2009 AASLD guidelines recommend reduced-dose PEG-IFNα2a (135 μg subcutaneously once a week) or PEG-IFNα2b (1 μg/kg subcutaneously once a week) and ribavirin (200-800 mg/day orally divided in two doses) for individuals with CKD stage 3, 4, or 5 (creatinine clearance < 60 mL/minute/1.73 m²) not requiring RRT²² (Table 1).

Treatment of HCV in Patients With CKD Requiring RRT. Data from a meta-analysis support the use of standard IFN over PEG-IFN in patients undergoing hemodialysis. Although the 28 studies included in the meta-analysis were not head-to-head comparisons of standard IFN and PEG-IFN (24 studies used standard IFN, and 4 used PEG-IFN), the two agents had comparable efficacy in patients with CKD undergoing RRT: the SVR rate was 39% with conventional IFN and 33% with PEG-IFN. The meta-analysis also suggested that standard IFN was better tolerated in patients undergoing dialysis, as evidenced by the 19% dropout rate (versus 27% with PEG-IFN).²⁴ These results, however, are contradicted by those from a subsequent randomized trial of 50 dialysis patients treated with either standard IFNα2a (3,000,000 U subcutaneously 3 times per week) or

PEG-IFNα2a (135 μg/week subcutaneously).²⁹ This study showed higher SVR rates in patients treated with PEG-IFN versus standard IFN (48% versus 20%); additionally, patients treated with PEG-IFN had a lower dropout rate (0% versus 20% for patients treated with standard IFN).²⁹ The 2009 AASLD guidelines recommend considering of HCV treatment in patients on dialysis with either standard IFN (IFNα2a or IFNα2b, 3,000,000 U subcutaneously 3 time per week) or reduced-dose PEG-IFN (PEG-IFNα2a, 135 μg/week subcutaneously, or PEG-IFNα2b, 1 μg/kg/week subcutaneously; Table 1).²²

Only limited data are available on tolerable ribavirin dosing in dialysis patients. Results from small uncontrolled trials suggest that the addition of fixed low-dose ribavirin (200 mg/day orally) to IFN therapy in patients undergoing hemodialysis enhances SVR rates.^{25,30-32} For instance, one study reported an SVR rate of 28.6% in dialysis patients (80% infected with HCV genotype 1a/1b and 20% infected with HCV genotype 2) who were treated with PEG-IFNα2a (135 μg/week subcutaneously) plus ribavirin (200 mg/day orally).³² These promising results, however, have not been corroborated by large randomized trials. Additionally, side effects were common with this regimen (mainly hematological and influenza-like symptoms), and the dropout rate was 71.4%.³² Other authors have described adjustments of the ribavirin dose to target plasma concentrations comparable to those reported in patients with normal renal function (7-17 μmol/L).^{26,30,31} However, there are some limitations to this approach. First, the optimal therapeutic plasma concentration of ribavirin is unknown; therefore, the extrapolation of plasma ribavirin concentrations from reference populations may have limitations. Second, assays for monitoring ribavirin plasma concentrations are not widely available, and ribavirin-induced hemolytic anemia may occur in hemodialysis patients despite the maintenance of apparently therapeutic plasma ribavirin levels.³⁰

The administration of ribavirin (regardless of the regimen) in patients undergoing hemodialysis typically requires the use of an erythroid-stimulating agent (ESA) such as erythropoietin or darbopoetin-α to correct anemia. A small study evaluating two different regimens of ESAs in 32 patients (59% with an HCV genotype 1 infection) who were undergoing

hemodialysis and were treated with PEG-IFN and ribavirin suggested that starting ESAs before antiviral therapy to maintain a hemoglobin level of 11 g/dL (a preventive strategy) was more effective than the introduction of ESAs after antiviral therapy had been started and hemoglobin levels had decreased to less than 10 g/dL (an adaptive strategy).³³ Although the preventive ESA strategy resulted in higher median hemoglobin concentrations (10.9 versus 9.6 g/dL) and higher median ribavirin doses (142 versus 105 mg/day) than the adaptive strategy, the difference in the SVR rates of the two groups was not statistically significant (45% and 58%, respectively, and 50% for the entire study population).³³

Treatment of HCV in Renal Transplant Recipients. The use of IFN-based therapy to treat HCV infection in renal transplant recipients is limited by well-founded concerns about inducing graft rejection due to its immune-modulating effects.²² Thus, IFN is contraindicated in renal transplant recipients, although some reports suggest that it can be used without jeopardizing the graft.^{34–36} In addition, the use of IFN may be contemplated in renal transplant recipients with fibrosing cholestatic hepatitis in an effort to prevent hepatocellular failure.²⁰

Direct-Acting Antiviral (DAA) Agents for the Treatment of HCV in Patients With CKD. The 2011 update of the treatment of HCV genotype 1 infections by the AASLD does not provide data on the use of DAA agents in patients undergoing RRT.³⁷ The addition of DAA agents to PEG-IFN and ribavirin significantly enhances SVR rates, but the pharmacokinetics and toxicity profiles of these agents in individuals with impaired renal function remain uncertain because registration trials have excluded patients with CKD.^{38–40} Additionally, the higher prevalence of baseline anemia is a major concern for the use of these agents in individuals with CKD. Data from premarketing trials showed an approximately 2-fold higher incidence of anemia when boceprevir or telaprevir was added to IFN and ribavirin in individuals with normal baseline hemoglobin concentrations (hemoglobin level > 12 g/dL for females and > 13 g/dL for males).^{38–40} Therefore, the decision to add one of the two currently licensed DAA agents (boceprevir or telaprevir) to PEG-IFN and ribavirin for the treatment of HCV genotype 1 infections in

patients with mild renal impairment (CKD stage 1 or 2) should be based on a patient-by-patient assessment of potential benefits, tolerability, and toxicity.

Preclinical data show that boceprevir and telaprevir undergo extensive hepatic enzymatic metabolism and are predominantly excreted in the feces (79%-82%) with minimal renal excretion (1%-9%).^{41,42} Therefore, the manufacturers of boceprevir and telaprevir do not recommend dose adjustments in patients with impaired renal function. Data from healthy volunteers indicate that hemodialysis removes less than 1% of administered boceprevir. The mean area under the curve after a single 800 mg dose of boceprevir was 10% lower in individuals with CKD undergoing hemodialysis versus individuals with normal renal function; however, no information is available about its use in individuals requiring RRT.⁴¹ After a single 750 mg dose of telaprevir in HCV-negative individuals with a creatinine clearance < 30 mL/minute/1.73 m², the area under the curve and the maximum serum concentration of this agent were increased by 21% and 3%, respectively, in comparison with individuals with intact renal function. Telaprevir, however, has not been studied in individuals undergoing RRT, and it remains unknown whether this agent is dialyzable by peritoneal dialysis or hemodialysis.⁴²

Conclusion

HCV infection has a detrimental effect on the survival of individuals with CKD. Although therapeutic options for HCV continue to evolve and have resulted in higher SVR rates, increased toxicity from multidrug regimens is an important concern. Therapeutic antiviral regimens for individuals with advanced stages of CKD and particularly for those on maintenance hemodialysis have suboptimal efficacy and are associated with significant toxicities. Therefore, it is crucial to identify and treat HCV during early stages of CKD when the tolerability of the best available antiviral regimens is acceptable and toxicity occurs less frequently, especially if the patient is potentially a candidate for renal transplantation. ■

CORRESPONDENCE

Andres F. Carrion, M.D., Department of Medicine, University of Miami Miller School of Medicine, 1201 Northwest 16th Street, Office B-1039, Miami, FL 33125. E-mail: acarriomonsalve@med.miami.edu

REFERENCES

1. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006;144:705-714.
2. Finelli L, Miller JT, Tokars JL, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 2002. *Semin Dial* 2005;18:52-61.
3. Perico N, Cattaneo D, Bikbov B, Remuzzi G. Hepatitis C infection and chronic renal disease. *Clin J Am Soc Nephrol* 2009;4:207-220.
4. Altraif IH, Abdulla AS, al Sebayel MI, Said RA, al Suhaibani MO, Jones AA. Hepatitis C associated glomerulonephritis. *Am J Nephrol* 1995;15:407-410.
5. Chan TM, Lok AS, Cheng IK. Hepatitis C infection among dialysis patients: a comparison between patients on maintenance hemodialysis and continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* 1991;6:944-947.
6. Fabrizi F, Poordad FF, Martin P. Hepatitis C infection and the patient with end-stage renal disease. *Hepatology* 2002;36:3-10.
7. Natov SN, Lau JY, Bouthot BA, Murthy BV, Ruthazer R, Schmid CH, et al. Serologic and virologic profiles of hepatitis C infection in renal transplant candidates. *Am J Kidney Dis* 1998;31:920-927.

8. Izopet J, Sandres-Sauné K, Kamar N, Salama G, Dubois M, Pasquier C, et al. Incidence of HCV infection in French hemodialysis units: a prospective study. *J Med Virol* 2005;77:70-76.
9. Johnson DW, Dent H, Yao Q, Tranaeus A, Huang CC, Han DS, et al. Frequencies of hepatitis B and C infections among haemodialysis and peritoneal dialysis patients in Asia-Pacific countries: analysis of registry data. *Nephrol Dial Transplant* 2009;24:1598-1603.
10. Chou CY, Wang IK, Liu JH, Lin HH, Wang SM, Huang CC. Comparing survival between peritoneal dialysis and hemodialysis treatment in ESRD patients with chronic hepatitis C infection. *Perit Dial Int* 2010;30:86-90.
11. Fabrizi F, Takkouche B, Lunghi G, Dixit V, Messa P, Martin P. The impact of hepatitis C virus infection on survival in dialysis patients: meta-analysis of observational studies. *J Viral Hepatitis* 2007;14:697-703.
12. Kalantar-Zadeh K, McAllister CJ, Miller LG. Clinical characteristics and mortality in hepatitis C-positive hemodialysis patients: a population-based study. *Nephrol Dial Transplant* 2005;20:1662-1669.
13. Butt AA, Khan UA, Skanderson M. Comorbidities and their impact on mortality in HCV and HCV-HIV-coinfected persons in dialysis. *J Clin Gastroenterol* 2008;42:1054-1059.
14. Fabrizi F, Martin P, Dixit V, Bunnapradist S, Dulai G. Hepatitis C virus antibody status and survival after renal transplantation: meta-analysis of observational studies. *Am J Transplant* 2005;5:1452-1461.
15. Lee WC, Shu KH, Cheng CH, Wu MJ, Chen CH, Lian JC. Long-term impact of hepatitis B, C virus infection on renal transplantation. *Am J Nephrol* 2001;21:300-306.
16. Ozdemir BH, Ozdemir FN, Sezer S, Colak T, Haberal M. *De novo* glomerulonephritis in renal allografts with hepatitis C virus infection. *Transplant Proc* 2006;38:492-495.
17. Bruchfeld A, Wilczek H, Elinder CG. Hepatitis C infection, time in renal-replacement therapy, and outcome after kidney transplantation. *Transplantation* 2004;78:745-750.
18. Morales JM. Hepatitis C virus infection and renal disease after renal transplantation. *Transplant Proc* 2004;36:760-762.
19. Mahmoud IM, Sobh MA, El-Habashi AF, Sally ST, El-Baz M, El-Sawy E, et al. Interferon therapy in hemodialysis patients with chronic hepatitis C: a study of tolerance, efficacy and post-transplantation course. *Nephron Clin Pract* 2005;100:c133-c139.
20. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl* 2008;109:S1-S99.
21. Gürsoy M, Güvener N, Köksal R, Karavelioğlu D, Baysal C, Ozdemir N, et al. Impact of HCV infection on development of post-transplantation diabetes mellitus in renal allograft recipients. *Transplant Proc* 2000;32:561-562.
22. Ghany MG, Strader DB, Thomas DL, Seeff LB; for American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009;49:1335-1374.
23. Martin P, Fabrizi F. Hepatitis C virus and kidney disease. *J Hepatol* 2008;49:613-624.
24. Fabrizi F, Dixit V, Messa P, Martin P. Interferon monotherapy of chronic hepatitis C in dialysis patients: meta-analysis of clinical trials. *J Viral Hepat* 2008;15:79-88.
25. Rendina M, Schena A, Castellana NM, Losito F, Amoroso AC, Stallone G, et al. The treatment of chronic hepatitis C with peginterferon alfa-2a (40 kDa) plus ribavirin in haemodialysed patients awaiting renal transplant. *J Hepatol* 2007;46:768-774.
26. Bruchfeld A, Stähle L, Andersson J, Schvarcz R. Ribavirin treatment in dialysis patients with chronic hepatitis C virus infection—a pilot study. *J Viral Hepat* 2001;8:287-292.
27. Dixit NM, Layden-Almer JE, Layden TJ, Perelson AS. Modelling how ribavirin improves interferon response rates in hepatitis C virus infection. *Nature* 2004;432:922-924.
28. Martin P, Jensen DM. Ribavirin in the treatment of chronic hepatitis C. *J Gastroenterol Hepatol* 2008;23:844-855.
29. Liu CH, Liang CC, Lin JW, Chen SI, Tsai HB, Chang CS, et al. Pegylated interferon alpha-2a versus standard interferon alpha-2a for treatment-naïve dialysis patients with chronic hepatitis C: a randomised study. *Gut* 2008;57:525-530.
30. Tan AC, Brouwer JT, Glue P, van Leusen R, Kauffmann RH, Schalm SW, et al. Safety of interferon and ribavirin therapy in haemodialysis patients with chronic hepatitis C: results of a pilot study. *Nephrol Dial Transplant* 2001;16:193-195.
31. Mousa DH, Abdalla AH, Al-Shoail G, Al-Sulaiman MH, Al-Hawas FA, Al-Khader AA. Alpha-interferon with ribavirin in the treatment of hemodialysis patients with hepatitis C. *Transplant Proc* 2004;36:1831-1834.
32. Carriero D, Fabrizi F, Uriel AJ, Park J, Martin P, Dieterich DT. Treatment of dialysis patients with chronic hepatitis C using pegylated interferon and low-dose ribavirin. *Int J Artif Organs* 2008;31:295-302.
33. Deltenre P, Moreno C, Tran A, Ollivier I, Provôt F, Stanke F, et al. Anti-viral therapy in haemodialysed HCV patients: efficacy, tolerance and treatment strategy. *Aliment Pharmacol Ther* 2011;34:454-461.
34. Konishi I, Horiike N, Michitaka K, Ochi N, Furukawa S, Minami H, et al. Renal transplant recipient with chronic hepatitis C who obtained sustained viral response after interferon-beta therapy. *Intern Med* 2004;43:931-934.
35. Rostaing L, Izopet J, Baron E, Duffaut M, Puel J, Durand D. Treatment of chronic hepatitis C with recombinant alpha 2b interferon in kidney transplant recipients: preliminary results and side effects. *Transplant Proc* 1995;27:948-950.
36. Tokumoto T, Tanabe K, Ishikawa N, Simizu T, Oshima T, Noguchi S, et al. Effect of interferon-alfa treatment in renal transplant recipients with chronic hepatitis C. *Transplant Proc* 1998;30:3270-3272.
37. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB; for American Association for Study of Liver Diseases. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011;54:1433-1444.
38. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al.; for SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1195-1206.
39. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al.; for HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1207-1217.
40. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al.; for ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;364:2405-2416.
41. Victrelis [package insert]. http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf. Accessed June 2012.
42. Incivek [package insert]. http://pi.vrtx.com/files/uspi_telaprevir.pdf. Accessed June 2012.