Treatment of Chronic Hepatitis C Infection in Patients With Renal Failure

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Patients with end-stage renal disease continue to have a high prevalence of hepatitis C virus infection despite screening of blood products and efforts to prevent the transmission of viral hepatitis within dialysis units. Although biochemical dysfunction often is absent in infected patients, an increased rate of mortality from liver disease has been observed in patients on long-term dialysis. In addition, hepatitis C–infected renal transplant recipients have diminished patient and graft survival rates compared with uninfected controls. Antiviral therapy with interferon in renal transplantation candidates has resulted in sustained viral responses that have been durable even after subsequent renal transplantation. Graft dysfunction remains a major concern, limiting the use of interferon after renal transplant. Ribavirin, which accumulates and cannot be removed by dialysis, and may induce hemolysis, generally has been avoided in patients with end-stage renal disease. In pilot studies, cautious use of reduced doses of ribavirin has been possible in this population with close monitoring of hematocrit levels and additional measures to enhance compensatory erythropoiesis.

Patients with end-stage renal disease (ESRD) on renal replacement therapy, especially hemodialysis (HD), continue to have a high prevalence of hepatitis C virus (HCV) infection despite screening of blood products and precautions to prevent the spread of viral hepatitis in dialysis units. HCV infection in this population is notable for the frequent absence of biochemical dysfunction despite viremia and histologic activity. HCV infection now has been implicated clearly in diminished patient survival on chronic hemodialysis and patient and graft survival after renal transplantation (RT). A small but growing body of literature has described successful antiviral therapy with interferon (IFN) in patients with ESRD with rates of sustained virologic response (SVR) comparable with patients with normal renal function. Importantly, SVR is durable even after subsequent renal transplant and therapeutic immunosuppression. Major concern persists about IFN-induced renal graft loss, effectively limiting its routine use to the pretransplant setting.

Hepatitis C Virus in Dialysis Patients

The prevalence of anti-HCV among patients undergoing regular HD in the United States was 7.8% in 2002.[1] However, many centers have reported a decrease in HCV prevalence in recent years, reflecting a number of factors including diminished blood product requirement in patients with ESRD because of erythropoietin use, highly successful efforts to exclude blood donors with HCV infection, and increased attention to preventing HCV spread within dialysis units. In a multinational cohort, the Dialysis Outcomes and Practice Patterns Study, which included centers in the United States, Japan, and western Europe, the presence of highly trained staff in dialysis units predicted lower HCV infection rates, reflecting the importance of adherence to precautions to prevent the spread of HCV in this setting.[2] Jadoul et al[3] reported a 50% decrease in anti-HCV seropositivity in Belgian dialysis units, comparing the early to late 1990s with a similar trend in most other western European countries surveyed, although its prevalence remained high in eastern Europe.

Routine third-generation serologic testing for HCV now accurately identifies infected hemodialysis patients, most of whom also are viremic by polymerase chain reaction; false-negative serologic testing had been more frequent with earlier-generation tests.[4] Polymerase chain reaction and branched DNA assays also are reliable in these patients and may be useful especially in early detection of HCV infection before seroconversion has taken place.

The natural history of HCV infection in the hemodialysis population is not well defined for a number of

Abbreviations used in this paper: ESRD, end-stage renal disease; ETR, end treatment response; GN, glomerulonephritis; HCV, hepatitis C virus; HD, hemodialysis; IFN, interferon; RT, renal transplantation; SVR, sustained virologic response.

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reasons.[4] Hemodialysis patients, by virtue of their comorbidities, have diminished long-term survival rates, and with the typically slow progression of HCV infection its most serious consequences, most notably decompensated cirrhosis and hepatocellular carcinoma, may not evolve during the shortened life span of an HCV-infected patient maintained on HD. Serial liver biopsy examination data on adequate numbers of ESRD patients with HCV infection generally are not available to assess disease progression. Although liver disease is recognized infrequently in this population, there is information about the development of at least some complications of cirrhosis in dialysis patients. Data from the Case Mix Severity Special Study of the US Renal Data System and the Lombardy Dialysis and Transplant Registry suggested that although cirrhosis is infrequent in the dialysis population (2% in the United States, 1.5% in Lombardy), the death rate for dialysis patients with cirrhosis was 35% higher in comparison with those without cirrhosis.[5] In addition, a multicenter study from the United States, Europe, Australia, and New Zealand showed that there is an excess of liver cancer in ESRD patients, most likely reflecting an increased prevalence of chronic viral hepatitis.[6] In other single-center, prospective studies, the mortality rate was higher in anti–HCV-positive chronic HD patients compared with seronegative controls.[7,8] A recent meta-analysis has confirmed that HCV-infected dialysis patients have a lower survival rate than uninfected patients on dialysis with chronic liver disease implicated in the worse outcomes.[9] Combining data from more than 2000 patients on chronic hemodialysis, HCV infection was associated with a relative risk of mortality of 1.57 compared with uninfected patients with hepatocellular carcinoma and cirrhosis, which are more frequent causes of death in HCV-seropositive patients.[9] HCV infection also has been implicated in the development of diabetes mellitus, which in turn may increase waiting list mortality in candidates for renal transplantation.[10]

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Despite the high prevalence of HCV infection in the hemodialysis population, indications for therapy remain ill defined. Concern about the ability of this population to tolerate IFN and more recently ribavirin has been a factor.

Interferon Therapy

There are no large-scale studies of antiviral therapy for HCV in ESRD patients and much of the available literature consists predominantly of small uncontrolled clinical trials of interferon monotherapy with at least some treated patients achieving an SVR (see Table 1). In a recent meta-analysis, 14 clinical trials were included, only 2 of which were controlled studies.[11] The mean overall estimated SVR was 37% (95% confidence interval, 28–48), with a drop-out rate of 17% (95% confidence interval, 10–28). The overall weighted estimate for SVR in patients with HCV genotype 1 was 30.6% (95% confidence interval, 20.9–48.0). In the minority of these trials ($n = 5$) using a more standard IFN regimen (3 MU, 3 × weekly, subcutaneous route), the overall mean estimate of SVR was 39% (95% confidence interval, 25–56). A meta-analysis performed by Russo et al[12] included 11 studies of HCV therapy in dialysis patients with an overall SVR of 33%, and for those with genotype 1 an SVR of 26%. Thus, the literature on monotherapy for HCV in the ESRD population indicates that therapy may be at least as effective as in the nonuremic population, albeit with a high rate of treatment discontinuation because of side effects, perhaps in part reflecting delayed IFN clearance. As described later, excellent SVR rates are possible in renal transplant candidates.

Table 1. Treatment of Chronic Hepatitis C Virus Infection in ESRD

	SVR rate, %
IFN alfa	33,[12] 37[11]
Combination IFN alfa/ribavirin	12.5[13]
Pegylated IFN	33.3[15]

Interferon Plus Ribavirin Therapy

Ribavirin therapy enhances SVR rates when used in combination with IFN in patients with normal renal function. However, there has been considerable reluctance to use ribavirin in patients with ESRD mainly because it causes hemolytic anemia in a population already prone to anemia. Furthermore, ribavirin and its metabolites accumulate in renal failure and are not removed by dialysis. However, Bruchfeld et al[13] provided information about its safe use in ESRD. They described the use of low-dose ribavirin, monitoring of plasma concentrations, and administration of high-dose erythropoietin to replete iron stores to aid in erythropoiesis. In a pilot study they treated 5 HCV-infected patients on regular HD and 1 patient on peritoneal dialysis with IFN alfa-2b plus ribavirin.[13] IFN alfa-2b was given initially as monotherapy at a dose of 3 MU 3 times weekly after dialysis for 4 weeks; thereafter low-dose ribavirin was added, starting at 200–400 mg/day for 6 months. Five