

Spectrum of Hepatitis C in Dialysis Patients

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Liver disease remains a significant cause of morbidity and mortality in patients with end-stage renal disease (ESRD) treated by dialysis or transplantation. (1) Once the hepatitis C virus (HCV) was cloned, it rapidly became evident that HCV was highly prevalent in patients with ESRD maintained on HD and that HCV transmission was occurring within HD units in the absence of other parenteral risk factors (i.e., blood transfusion or illicit drug use). A number of other important facets of HCV infection in ESRD patients have been recognized, including false-negative serologic tests and an absence of biochemical dysfunction despite viremia.

Natural History of HCV in Dialysis Patients: HCV infection in dialysis patients is usually asymptomatic with an apparently indolent course. The natural history of HCV in this population, however, remains to be defined because, typically, HCV's course extends over decades rather than years, whereas dialysis patients generally have higher morbidity and mortality rates than those of the general population due to age and comorbid conditions making the long-term consequences of HCV infection difficult to establish. The evaluation of HCV is further complicated in the population by the observation that aminotransferase values are typically lower in dialysis patients than the nonuremic population. Dialysis patients who are HCV viremic have aminotransferase levels greater than those without, although values are still typically within the "normal" range.

A recent international collaborative survey from Europe, Australia, New Zealand, and the United States reported that the overall risk of cancer is increased in ESRD patients on dialysis compared with the general population. (2) The investigators found an excess of liver cancer (standardized incidence ratio 1.5, 95% CI 1.3-1.7), most likely related to the prevalence of infection with chronic HBV and HCV. Another study on mortality of HCV in dialysis has been reported by Nakayama et al. (3) who prospectively studied 1,470 chronic HD patients from 16 centers in Japan over a 6-year follow-up (1993-1999). Anti-HCV seropositivity was an independent risk factor for death (relative risk, 1.57; 95% CI 1.23-2.00, $P < .001$). Hepatocellular carcinoma accounted for 5.5% of all deaths in the group of anti-HCV-positive patients compared with none in the anti-HCV-negative group (5.5% vs. 0%, $p < .001$). Cirrhosis was documented in 8.8% and 0.4% of patients who died in the anti-HCV-positive and HCV-negative groups, respectively ($P < .001$). Thus at least some deaths occurring in HCV-infected patients on HD are clearly related to cirrhosis.

Whether the outcome for HCV patients remaining on dialysis is different from those who undergo renal transplant (RT) has been addressed in a retrospective study of 25 HCV-positive HD patients awaiting RT and 33 anti-HCV positive allograft recipients. (4) The groups were similar with respect to age, race, time on dialysis, underlying nephropathy, biochemical liver tests, and prevalence of heart disease. The transplant recipients were more often male. Survival was significantly lower ($P = .043$) in the group of anti-HCV-positive patients who were acceptable candidates but had not yet received a transplant. These observations are similar to those of Wolfe et al. (5) who performed a longitudinal study of mortality in 228,552 patients with ESRD on dialysis in the United States and they observed that the mortality ratio for dialysis patients who were listed for RT was 38% to 58% lower than that for all patients on dialysis, reflecting in part that transplant candidates are a more robust group. Although in the first postoperative month, recipients of a first cadaveric renal transplant had an initially higher risk of death than those who remained on dialysis; the subsequent long-term mortality rate was 48% to 82% lower in the RT recipients.

Liver Biopsy Data in Dialysis Patients: Only a few investigators have evaluated histologic severity of liver disease in HCV-positive patients with ESRD. In one report, 37 patients, anti-HCV positive evaluated for RT, most of whom were already dialysis-dependent, underwent liver biopsy. (6) Mild or moderate necroinflammatory activity occurred in all patients; bridging fibrosis was present in 3 of 37 (8%), and frank cirrhosis in 9 (24%). No relationship between severity of histologic changes and HCV viral load or genotype or aminotransferases activity was apparent. In this study, a history of alcohol abuse was elicited in 38% of patients, perhaps accounting in part for the frequency of advanced fibrosis. Sterling et al. evaluated liver histology in 50 consecutive patients with chronic HCV awaiting RT. (7) Bridging fibrosis or cirrhosis was present in

22%, which was not significantly different from a control group of HCV-positive patients with intact renal function and normal ALT, although there was trend toward more fibrosis in the dialysis group. In contrast, bridging fibrosis or cirrhosis was present in 49% of the other control group of HCV-positive patients with normal renal function and elevated ALT levels. Aminotransferase levels were not significantly different in the RT candidates compared with normal ALT controls. A risk factor for more extensive fibrosis in the RT candidates was a prior renal graft. These studies indicate that advanced fibrosis is a common histologic finding in individuals otherwise believed to be acceptable RT candidates despite "normal" aminotransferases levels. As in other studies of HCV in ESRD, patients evaluated for possible RT are generally a more robust cohort than dialysis-dependent patients as a whole. Patients with clinically overt liver disease might be precluded from RT evaluation, perhaps helping to underestimate the consequences of HCV in ESRD.

Conclusion: Potentially significant liver disease due to HCV occurs in HCV infected in ESRD and may be recognized only in liver biopsy. Longer term projective studies are needed in the population.

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