

Peginterferon Therapy of Hepatitis C in ESRD

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Chronic hepatitis C (HCV) is common among patients with end stage renal disease, with an estimated prevalence of 10% in hemodialysis patients (1). The high prevalence of HCV among dialysis patients can be attributed to several risk factors, including the number of blood transfusions, needle stick injuries, lack of adherence to infection control practice in dialysis units, transmission through dialysis machines and ultrafiltrates. Compared to hemodialysis, peritoneal dialysis has a lower risk of HCV infection.

Studies on the natural history of hepatitis C suggest that 50%-85 % of patients with acute HCV infection develop chronic HCV and up to 20% of patients with chronic HCV develop cirrhosis over a 20 year period. Data on the natural history of hepatitis C in patients with end stage renal disease are scarce, but cross-sectional data suggest that those with chronic HCV may have significant liver disease. Although patients on dialysis tend to have milder liver disease and normal liver enzymes compared to patients with normal renal function, patients with end stage renal disease and chronic hepatitis C may have severe chronic hepatitis on liver biopsy. Ten to 20% of patients will have bridging fibrosis or cirrhosis on liver biopsy (2).

Prospective trials of interferon monotherapy in dialysis patients with chronic hepatitis C demonstrate sustained response rates of 19%-63% and randomized trials report sustained response rates of 14%-37% (3). Higher doses of interferon have not resulted in greater efficacy and have led to higher drop out rates. Adverse events leading to drug discontinuation in decreasing order of frequency include flu-like symptoms, neutropenia, depression, and neurological symptoms. Drop out rates with 3 MU TIW range from 0-51%, with most studies reporting rates between 20-30%.

Identifying individuals with chronic hepatitis C on dialysis is important because patient and graft survival may be lower in infected recipients. Although studies following subjects with chronic hepatitis C after renal transplantation demonstrate no difference in 5-year patient and graft survival compared to uninfected individuals, studies following subjects for longer periods of time have demonstrated lower survival in those with hepatitis C. A study of 834 renal transplant patients demonstrated that hepatitis C accounts for most of the liver disease following kidney transplantation (4). In a separate cohort, cadaveric kidney transplant recipients with anti-HCV antibodies had a significantly shorter patient and graft long-term survival than recipients without antibodies (5). The overall mortality was 13.4% for anti-HCV-positive patients compared to 4.9% in anti-HCV-negative patients ($p<0.01$), and liver mortality was 5.4% in anti-HCV-positive patients compared to 0.3% in anti-HCV-negative patients ($p<0.001$).

Treatment of HCV after kidney transplantation with interferon may increase the risk of graft rejection and interferon is used with caution after transplant. Thus, identifying effective therapy prior to kidney transplantation is important. Ribavirin may be poorly tolerated in dialysis patients because it is associated with hemolytic anemia and many dialysis patients are already anemic.

Based upon prior literature of unmodified interferon monotherapy in dialysis patients, we designed a multicenter randomized trial of pegylated interferon monotherapy in patients on dialysis with chronic hepatitis C. Studies of interferon monotherapy, 3 million units three times a week, demonstrate reasonable efficacy with tolerable side effects. Doses of 5 - 6 MU TIW, lead to higher dropout rates without any improvement in sustained response (by intention to treat). These data suggest that low to moderate doses of pegylated interferon alpha-2b may lead to a reasonable sustained response with an acceptable side effect profile.

Our study design is a multicenter trial randomizing subjects with chronic hepatitis C on dialysis to pegylated interferon alpha 2b 0.5 ug/kg or 1.0 ug/kg for 48 weeks. Treatment duration is not stratified by genotype. We anticipate that 84 subjects will complete the study. In contrast to prior studies, subjects are treatment naive without a history of organ transplantation. Diabetes must be well controlled and subjects are excluded if they have proliferative retinopathy. The primary endpoint is

sustained viral response measure by a commercial PCR assay. The secondary endpoint is normalization of ALT. Enrollment has just begun.

References

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