

Ribavirin and Peginterferon for Hepatitis C in ESRD

Bruce A. Luxon, MD PhD



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Hepatitis C virus (HCV) infection is a major problem among patients undergoing chronic hemodialysis (HD). Some recent studies analyzing liver histological characteristics of HD patients infected with HCV have shown significant chronic liver disease, including chronic active hepatitis or advanced cirrhosis in 60% to 70% of the patients who were anti-HCV positive (1). Thus, eradication of HCV infection in patients with end-stage renal failure may reduce the progression of liver disease in renal allograft recipients, as well as the risk for potential transmission of HCV within HD units (1).

There are two pilot studies looking at the use of standard interferon alfa 2b in combination with ribavirin in patients with end stage renal disease requiring hemodialysis. Bruchfeld et al (2) treated five hemodialysis patients and one peritoneal dialysis patient with chronic hepatitis C with interferon-alfa-2b 3 MIU thrice weekly (TIW) for 4 weeks, where after ribavirin 200-400 mg was added, for an intended total treatment of 28 weeks. Four patients completed the treatment, one withdrew after 16 weeks due to interferon side effects and another developed heart failure and died after 14 weeks, which was not considered treatment related. A target serum concentration of ribavirin was set at 10-15 $\mu\text{mol/l}$, based on patients with normal renal function. The average daily ribavirin dose was 170-300 mg. Hemoglobin levels between 9.5 and 11.0 g/dl were maintained throughout the treatment period using erythropoetin (20-30,000 IU/week) and blood transfusions were avoided.

Bruchfeld et al found a virological response with 5/6 patients becoming HCV- RNA negative during treatment, but four relapsed post-treatment. Due to the HCV genotype, (all patients were genotype 1) these patients might have benefited from a longer treatment period. They concluded that ribavirin, in combination with interferon-alfa, can be used to treat dialysis patients with HCV. Anemia was a main side effect and was managed successfully with reduced ribavirin doses, close monitoring of circulation ribavirin concentrations and hemoglobin as well as high-dose erythropoetin and intensified iron therapy.

A second study by Tan et al (3) studied five patients (three females, two males; age range 22-65 years) with hepatitis C, who were on chronic hemodialysis. Prior to and during the study, all patients received erythropoetin. Blood transfusions were permitted if clinically required. Treatment consisted of open-label subcutaneous interferon alfa-2b 3 MIU TIW plus oral ribavirin for 40 weeks. The initial ribavirin dose was 200 mg/day, which could be increased by 200 mg every 6 weeks depending on the hemoglobin response (less than 10% reduction from baseline). Trough plasma ribavirin concentrations were obtained every 4-6 weeks and measured by a validated high performance liquid chromatography/mass spectrometric (HPLC/MS) assay (3).

In all 5 patients treated the hemoglobin level dropped. Despite increasing doses of erythropoetin and transfusions, 2 patients had to discontinue ribavirin after 7 weeks. Two other patients were able to tolerate ribavirin at 200 mg TIW. The fifth patient remained at a dose of 200 mg daily. Ribavirin plasma levels were 2517 and 1594 ng/ml at doses of 200 mg daily and TIW, respectively. In comparison, patients with normal renal function taking ribavirin 1200 mg daily had serum levels of 2300 ng/ml (4).

Four of five patients achieved undetectable HCV RNA during treatment. Three of the four responders had undetectable HCV RNA by week 4. The fourth patient cleared the virus by treatment week 16. No data is available for sustained virological response in these patients.

In both of these studies combination therapy with standard interferon and ribavirin suppressed HCV-RNA in the majority of hemodialysis patients. The authors concluded that a high percentage of sustained response is possible in this difficult-to-treat patient group. As noted by both Bruchfeld and Tan (2,3), ribavirin-induced anemia was an important problem that could be ameliorated by ribavirin dose reductions and the use of erythropoetin.

A multi-center randomized trial of pegylated interferon alfa-2b alone versus pegylated interferon alfa-2b plus ribavirin for 48 weeks is being conducted at 4 sites. Anticipated enrollment is 60 patients. The primary endpoints are sustained biochemical and virological response. The safety and tolerability of these two regimes in hemodialysis patients with hepatitis C will also be assessed. Pegylated interferon alfa-2b is given 1 µg/kg weekly after dialysis. Ribavirin is given in syrup form, starting at 3 mg/kg per week and adjusted to keep hemoglobin >9.5 g/dl.

References

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