Hepatitis C Virus and Renal Failure

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HEPATITIS C virus (HCV) is an RNA virus with great diversity. During replication, it lacks proofreading; therefore, it is an error-prone virus. This slow pathogen takes about 20 years to cause liver disease. There are six major genotypes and more than 100 subtypes. The clinical significance and natural history of the disease in relation to genotype and subtype are controversial. However, there is evidence to suggest that genotypes 1 and 4 have a poorer prognosis, while genotypes 2 and 3 have better response rates to interferon. Worldwide, 170 million people are infected with HCV; 20% of these will progress to liver failure. Because it is a disease that takes two to three decades to cause end-stage liver failure and blood/organ donors have been screened routinely only in the last decade, the disease is expected to peak around the year 2010 to 2012. The modes of transmission of the disease are parental and, to a lesser extent, sexual. Besides hepatic damage, HCV may be associated with the development of mixed cryoglobulinemia, vasculitis, mesangioproliferative glomerulonephritis, and membranous nephritis. Currently, 10.4% of patients on dialysis in the United States are HCV positive, many of whom display normal liver function tests. The incidence is higher in other parts of the world. There are reports to suggest that the 2-year patient survival among HCV+ patients undergoing kidney transplantation (KTx) is better than that on dialysis.[1]

TREATMENT OPTIONS

Treatment for HCV for patients with normal renal function consists of interferon-α (INF), INF with ribavirin, PEGylated INF, or PEGylated INF plus ribavirin.

INF

INF has antiviral and immunomodulatory activity. It increases HLA expression as well as augments the functional activity of cytoxic T cells, natural killer cells, and macrophages.[2,3] In randomized, placebo-controlled, double-blinded studies, INF treatment was effective for chronic hepatitis in nontransplant patients.[4–7] In renal transplant patients, however, INF has been associated with an increased incidence of rejection and graft loss as first demonstrated by Kramer et al[8] and by Kovacik et al,[9] who used INF to prevent cytomegalovirus infection. At least 12 reports have confirmed the initial observation, the drug is relatively contraindicated after kidney transplantation.[10–17] Slater et al[18] reported in a heart transplant rat model a dose-dependent increase in the rate and severity of acute rejection; however, clinical liver transplantation (LTx) patients have been able to tolerate INF with a minimally increased risk of acute rejection when adequate baseline immunosuppression is maintained. Thus, INF has remained a useful therapy for HCV recurrence after liver transplantation.

RIBAVIRIN

Ribavirin is a guanine analogue, which interferes with nucleoside synthesis. It has a broad spectrum of activity, affecting both DNA and RNA viruses.[20] It binds to red cells, with saturation occurring in 4 weeks. The drug is cleared by the kidney and is nondialyzable.[21,22] The use of ribavirin alone produces a biochemical response rate of 50% among patients with hepatitis. However, this response is neither sustainable nor associated with viral clearance. In addition, a dose-dependent hemolytic anemia has been described.

COMBINATION OF INF AND RIBAVIRIN

A prospective, placebo-controlled, randomized trial of a 48-week course of therapy resulted in a 38% to 41% sustained virological response among immunocompetent patients. Patients with low viral loads, genotypes 2 or 3, ages <40 years, and women are better responders. This regimen has been used after liver transplantation for the last 3 to 4 years with increasing regularity.

PEGYLATED INTERFERON

PEGylated INF is INF conjugated to polyethylene glycol (PEG). This prevents the rapid degradation of interferon, increasing its half-life. There are two types: PEG-INF2a and PEG-INF2b. Both preparations have increased half-lives of 96 and 45 hours, respectively. When used in patients with HCV infection in randomized trials, they have shown superior efficacy by virtue of their pharmacokinetics and pharmacodynamic mechanisms. Sustained and superior responses were confirmed in both cirrhotic and noncirrhotic populations.[23–25] Currently, several single-center and multicenter trials in pre- and postliver transplant patients are underway to evaluate the responses and, at the same time, distinguish favorable prognostic factors.

HCV: RENAL FAILURE

Ribavirin in this setting is not recommended because the drug is not cleared by dialysis. However, extremely low doses, 200 mg once or twice a week, have been used in a few series. INF-α is the only noncontroversial option. Interestingly, the response rates are much higher compared with those in nondialysis patients, including histologic improvement in up to 82% of patients.[26,27] The response, both virologic and histologic, begins 2 to 3 months after starting treatment. The reason for this improved response is not clear. The fibrosis score and iron load influence the response rate. INF therapy is, therefore, strongly suggested in patients who are on dialysis and awaiting KTx in order to reduce the viral load because INF is difficult to use after KTx. We are in the process of conducting prospective trials with low-dose (200 mg once a week) ribavirin and PEG interferon in HCV+ patients who are awaiting renal transplantation.

KIDNEY TRANSPLANTATION AFTER LIVER TRANSPLANTATION WITHIN HCV+ PATIENTS

We have reported 17 HCV+ patients who underwent KTx 58 ± 32 months post-LTx. The mean viral load was 440 ± 661 × 10⁹ or 10⁶ copies/mL. Twenty-nine acute rejection episodes (1.7 per patient) were treated with increased steroids, leading to a transient rise in LFTs. One patient underwent retransplantation 3.7 years post-KTx and 12.7 years post-LTx. Four patients died of lung carcinoma ($n = 2$), pancreatitis ($n = 1$), and noncompliance ($n = 1$).[28]

SUMMARY

It is difficult to treat HCV infections after KTx. Pre-KTx PEG-INF for six months should provide a sustained viral and histological response. An extremely small dose of Ribavirin (200 mg once a week) may be used pre-KTx, but it is not yet clear that this will be safe. Post-KTx INF cannot be used, and small doses of Ribavirin produce poor and only transient responses. Kidney transplants are still associated with a better survival rate than dialysis for HCV+ dialysis patients, provided that there are no signs of liver failure, such as ascites, encephalopathy, and/or coagulopathy and that the HAI is ≤ 6 and the fibrosis score is ≤ 1. However, an occasional occurrence of liver failure post-KTx cannot be excluded, since the natural history of HCV is altered with immunosuppression, particularly if antilymphocyte preparations are used. There is some suggestion from post-LTx patients that there may be a benefit of new immunosuppressive combination regimens that include an IL2 receptor antagonist and mycophenolate mofetil (MMF), which may have a wide spectrum of antiviral property without steroids but this claim is controversial. These regimens need further exploration.

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