

Successful Treatment of Hepatitis C Virus in a Renal Transplant Recipient; Case Report and Review of the Current Literature

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Citation

E Kim, J Ford, S Alkhowaiter, E Yoshida. *Successful Treatment of Hepatitis C Virus in a Renal Transplant Recipient; Case Report and Review of the Current Literature*. The Internet Journal of Gastroenterology. 2010 Volume 10 Number 2.

Abstract

We report a case of a 56 year old man with chronic hypertension, who was found to have nephrotic range proteinuria and a serum creatinine of 800 $\mu\text{mol/L}$. Bilateral "small kidneys" were reported on renal ultrasound, but renal biopsy was not performed at this time. We describe the clinical course and discuss the medical measures taken

CASE HISTORY

A 56 year old man with chronic hypertension, was found to have nephrotic range proteinuria and a serum creatinine of 800 $\mu\text{mol/L}$. Bilateral "small kidneys" were reported on renal ultrasound, but renal biopsy was not performed at this time. Peritoneal dialysis was initiated, requiring a change to intermittent hemodialysis due to development of fungal peritonitis. "Cryptogenic" chronic hepatitis C virus (HCV) was diagnosed after a positive anti-HCV antibody test, with confirmatory HCV RNA (genotype 3A). A liver biopsy was performed during the transplant assessment showing grade 1 inflammation and fibrosis, with minimal piecemeal necrosis, and an abdominal ultrasound reported a "fatty liver", without any changes consistent with cirrhosis. Hepatitis B, HIV, and other tests for chronic liver disease were negative. An evaluation by a hepatologist was requested for potential treatment of HCV prior to renal transplant. Given normal liver enzymes with only grade 1 fibrosis, and the inherent risks of treatment in patients with ESRD, not felt to have indication for pegylated interferon and ribavirin.

He underwent uncomplicated cadaveric renal transplant from a HCV positive donor. Post-operative course complicated by primary renal graft nonfunctioning, required hemodialysis during same hospitalization. Renal transplant biopsy was performed, showing acute tubular necrosis and "borderline" acute rejection. The patient was maintained on mycophenolate mofetil 500 mg BID and tacrolimus 4 mg am, 3 mg pm. He then developed elevation of liver enzymes

post-transplant, (ALT 113, AST 55, GGT 573, ALP 129), felt to be secondary to increased HCV activity due to transplant immunosuppression. He was treated several months later for pulmonary tuberculosis, treated with ethambutol, moxifloxacin, streptomycin, rifampin for 2 months and with ethambutol, rifampin for 9 months.

A follow-up biphasic CT scan described the liver as lobulated, with atrophy of the right lobe and hypertrophy of the left and caudate lobes, and features of portal hypertension including splenomegaly, splenic and gastric varices. Endoscopy was subsequently arranged, with no evidence of esophageal or gastric varices. A liver biopsy was performed that reported stage 3 fibrosis (ie. incipient cirrhosis). Liver function tests at this time did not reveal any evidence of decompensated cirrhosis, with no associated hepatic encephalopathy. (ALT 18, AST 19, GGT 32, total bilirubin 25, INR 1.1 and albumin 46). Due to liver cirrhosis, he was then initiated on screening for hepatocellular carcinoma with a liver ultrasound every 6 months. A discussion was initiated with patient and family due to rapid progression of liver fibrosis, the risks of HCV related cirrhosis, as well as the benefits and risks of HCV treatment, including renal allograft rejection. After agreement from the patient and family, he was started on pegylated interferon alpha 2a 180 mcg weekly and ribavirin 400 mg BID, planned for 24 weeks treatment.

Several weeks after treatment initiation, the patient was admitted to a community hospital for dehydration due to diarrhea and decreased oral intake, felt to be resulting from

side effects from interferon and ribavirin. Bloodwork led to a diagnosis of acute renal failure with an elevated serum creatinine at 183 (baseline 125 to 135). The serum creatinine subsequently improved with intravenous fluids. Interferon was held for 1 week due to development of stomatitis (HSV culture negative) and pancytopenia (Hb 86, WBC 2.2, platelets 109). Persistent anemia required transfusion of 4 units of packed red blood cells during hospitalization with a hemoglobin level of 115 on discharge. Ribavirin dosage was decreased to 600 mg daily from 800 mg daily due to significant anemia. Several months after discharge from this hospitalization, developed recurrence of anemia and pancytopenia, with WBC 1.5, neutrophils 0.9, Hb 84 requiring transfusion of 2 units of packed red blood cells. Hospitalization was not required, and was found to have normalization of liver enzymes with ALT 25, AST 26 and total bilirubin of 19, and stable renal function with a serum creatinine of 132. Ribavirin dosage required further reduction to 200 mg BID due to recurrent anemia, and persistent red blood cell transfusion requirements due to symptomatic anemia with Hb levels dipping to the low 80's. Another hospitalization was necessary for several days due to worsening symptomatic anemia and volume depletion due to decreased oral intake. Transfused 4 units total during admission with packed red cells for a Hb of 70.

HCV RNA level was negative at 4 and 12 weeks after initiation of HCV treatment, as well as a sustained virological response, with an undetectable HCV RNA, 6 months after completion of peg-interferon and ribavirin. Normalization of liver enzymes occurred during treatment, along with resolution of transfusion-dependent anemia after completion of therapy. Renal function remained stable after treatment, with serum creatinine levels close to pre-treatment baseline levels.

DISCUSSION

Recipients of extra-hepatic organ transplants with chronic hepatitis C (HCV) infection pre-transplant can develop progressive post-transplant liver disease, which is well reported to be a significant cause of morbidity and mortality. 7 to 24 percent of renal transplant (RT) patients are found to have serum liver biochemical abnormalities, and liver failure is determined to be the cause of death in 8 to 28 percent of post-renal transplant recipients.^{1,2} A major concern in these transplant recipients is the onset of an aggressive and rapid course of HCV-related infection and liver disease, facilitated by ongoing immunosuppression to prevent graft rejection.^{3,4}

Transplant associated immunosuppression has been reported to cause increased hepatitis C replication in addition to a range of liver-related complications such as chronic active hepatitis, fibrosing cholestatic hepatitis, fulminant liver failure and hepatocellular carcinoma. Organ transplant recipients with hepatitis C have been shown to have significantly worse 10-year graft and patient survival rates, and avoiding excessive immunosuppression has been suggested to minimize the risk of hepatitis C reactivation. Treatment options include interferon-alpha in combination with ribavirin, approved for both initial treatment and relapse of chronic hepatitis C, as this has obtained the best results to date.⁵⁻⁷ However, the natural history of hepatitis C infection after extra-hepatic solid organ transplants is still incompletely understood, and treatment of chronic hepatitis C in this population remains challenging and is an area of ongoing research.

Renal transplant recipients with chronic hepatitis C have been studied more extensively than other solid organ transplants. The prevalence of chronic hepatitis C virus in dialysis patients is reportedly as high as 10% to 50% in the US⁸⁻¹¹. In the kidney transplant population, chronic hepatitis C infection is also very common, with prevalence ranging from 5% to 46%, depending on the country and/or centre, with the frequency of HCV much higher in RT patients from less-developed countries.¹²⁻¹⁶ The prevalence of anti-HCV-positive patients is influenced by various factors such as race, geographic origin of the recipient type (hemodialysis versus peritoneal dialysis) and duration of dialysis before transplantation, number of blood transfusions, history of previous transplants, and positivity for HBV infection.¹⁷⁻¹⁹ Although most studies on the long-term impact of chronic HCV infection on renal transplant suggests worse graft and patient survival, data comparing outcomes with HCV-negative transplant recipients is conflicting. Earlier studies showed worsening of liver disease in HCV-positive kidney transplant recipients, as immunosuppression prevents clearance of the virus, leading to increased HCV replication and liver-related disease.^{11,20-22} Morales et al. found that the survival of HCV-positive renal transplant patients was significantly lower than that of HCV-negative patients.^{23,24} RT recipients with chronic HCV can have an accelerated progression of liver disease leading to liver failure, which was the fourth leading cause of mortality (8-28%) in long-term survivors after renal transplantation.¹ Various investigators have speculated that this decreased survival might also be related to an increased risk of cardiovascular

disease, post-transplant diabetes mellitus, and sepsis.^{2,9,25,26} HCV also has been associated with reduced renal graft survival. HCV-related de novo glomerulonephropathy is likely responsible for the decrease in renal allograft survival in HCV positive patients compared to HCV negative patients, and chronic HCV infection contributes to the development of chronic allograft nephropathy.^{23,27,28} However, more recent studies have documented a relatively slow progression of liver fibrosis in this population.^{29,30} Despite increased liver and sepsis-related deaths in HCV-positive renal transplant recipients, renal transplantation improves overall survival in HCV+ patients on hemodialysis.³¹ Therefore, renal transplant remains as the best therapy for end-stage renal disease patients on renal replacement therapy who are known to be HCV positive.

Currently, the combination of pegylated-interferon-alpha and ribavirin is the mainstay of treatment for HCV in patients with normal renal function.^{6,7} In the HCV-positive renal transplant population, this treatment requires careful consideration. Transplant immunosuppression leads to significantly higher HCV viremia than pre-transplant values.^{1,32} In addition, the application of interferon-alpha after renal transplantation has been complicated by the onset of acute rejection, thus limiting its use in this population. IFN-alpha used for immunoprophylaxis of cytomegalovirus (CMV) infection in renal transplant recipients in the 1980's was associated with a high incidence of steroid-resistant allograft rejection, resulting in graft loss. Graft rejection, found in about 50% of patients, was mainly related to acute vascular rejection.^{33,34} In addition to its antiviral activity, IFN-alpha exerts anti-proliferative and immunomodulatory properties which have been associated with an increased risk of inducing or facilitating acute steroid-resistant rejection in allograft recipients.³⁵

IFN monotherapy has been used to treat HCV-positive RT recipients, with about half of these patients showing improvement in aminotransferases and about 25% eradicating HCV RNA. However, only a minority had a sustained virological response (SVR).³⁶⁻⁴⁰ A concerning complication was the development of acute cellular or humoral rejection seen more frequently amongst IFN-alpha treated patients, with many series documenting high rates of renal failure and graft loss (despite aggressive immunosuppressive therapy).⁴¹⁻⁴⁴ This association of acute renal failure and graft rejection in renal transplant recipients treated with interferon for chronic HCV has led to the

recommendation that patients with a renal transplant should not be given interferon alpha.^{5,45-47} Therefore, the limited efficacy of IFN-alpha, together with its high cost and risk of acute rejection have diminished the enthusiasm for its widespread use in renal RT recipients with chronic HCV infection. However, interferon treatment may be considered for select patients with worsening chronic active hepatitis (e.g. advanced fibrosis/cirrhosis or fibrosing cholestatic hepatitis C) and HCV-related glomerular disease after renal transplantation.^{23,48-50} The potential benefits of IFN therapy after RT should be weighed carefully against the risk of graft rejection and the decision should be made on an individual basis.

Due to the inherent challenges of treating hepatitis C after renal transplantation, many experts have advocated initiating hepatitis C treatment prior to renal transplantation.⁵¹⁻⁵⁴ Studies of dialysis patients who were successfully treated before transplantation indicated that HCV eradication is maintained after transplantation. In 1998, Rostaing et al. reported that the clearance of chronic hepatitis C by interferon was about half as effective in dialysis patients as compared to non-uremic patients.⁵⁵ However, other studies have shown that in hemodialysis patients, treatment with IFN-alpha is associated with a sustained biochemical and virological response that ranges from 20 to 90%.⁵⁶⁻⁵⁹ In one study of 78 HCV-positive patients who underwent renal transplantation, 15 were treated with IFN-alpha for one year prior to transplantation.⁵⁹ Of 15 patients treated with interferon-alpha, 10 (67%) had become HCV-RNA negative by the time of transplantation. In comparison, only 29% of the 63 untreated allograft recipients were HCV-RNA negative at the time of transplantation, and 12 (19%) developed de novo glomerulonephritis (all 12 patients were HCV-RNA positive at the time of transplantation).⁵⁹ Furthermore, IFN-alpha treatment of anti-HCV positive patients undergoing hemodialysis seems to have a beneficial effect on the course of liver disease following renal transplant, regardless of virological response.⁶⁰ At present, data on the relapse rate among RT recipients treated with IFN-alpha for HCV infection prior to transplantation remains limited and controversial. Controlled studies will be required to evaluate the long-term effects of this strategy on the course of liver disease, rates of transplantation, and graft and patient survival. However, based on available data, experts have suggested that interferon-alpha treatment be strongly considered in HCV-infected dialysis patients who are candidates for renal transplantation.^{51-53,61}

Currently, there is limited published data on the outcomes after treatment with peg-IFN in HCV-infected hemodialysis patients awaiting renal transplantation. In a study by Casanovas-Taltavull T. et al, peg-IFN had limited efficacy in this group, with an end of treatment (ETR) virologic response in 83%, sustained virologic response (SVR) in only 25%, and HCV recurrence in 50%. Tolerance was poor, with 4/12 (33%) discontinuing treatment due to adverse events, personal decision, or death.⁶² Large randomized controlled studies are needed to determine the role of peg-IF treatment in this population. Ribavirin has not been recommended for patients with a creatinine clearance below 50 mL/min, as it is renally excreted, with its metabolites not removed by hemodialysis. Ribavirin in dialysis patients is associated with a high risk of severe hemolytic anemia. However, some experts have supported the use ribavirin in renal dysfunction with close therapeutic drug monitoring, dosage adjustment and erythropoietin use when anemia develops.^{63,64} Combination therapy with IFN-alpha plus ribavirin in HCV-infected dialysis patients has been evaluated in several small studies. These authors also documented the safe use of ribavirin with dose adjustment, erythropoietin and close monitoring of hemoglobin levels.⁶⁵⁻⁶⁷

Several small studies have evaluated the use of peg-IFN in the renal transplant population. One study switched three patients from IFN to peg IFN during treatment, without development of renal allograft rejection.⁴⁴ A retrospective study by Baid et al. identified twelve HCV-positive renal transplant recipients who had been treated with IFN (1.5 to 3 million units three times weekly) plus/minus ribavirin (200 to 800mg/day) for biopsy proved chronic HCV. In three patients, interferon was subsequently changed to pegIFN (with ribavirin) at a dose of 1-1.5 mcg/kg once weekly without the developing graft rejection. More recently, Mukherjee et al. reported a patient with combined liver/kidney transplant (for decompensated cirrhosis from HCV genotype 1 complicated by hepatorenal syndrome requiring hemodialysis) who maintained normal renal function during treatment of recurrent HCV with peg-IFN 2a 180mcg/week and ribavirin 1200mg/day for 48 weeks. Immunosuppression was maintained with tacrolimus and prednisone. No adverse effects were reported and renal function remained stable. Biochemical and virological response were sustained at the end of treatment and six months afterwards. The patient continued to have normal liver biochemistry and serum creatinine, and remained HCV RNA negative eighteen months after treatment.⁶⁸

Montalbano et al. reported a case of a 57 year old male with a liver/kidney transplant who underwent successful treatment of cryoglobulinemia with pegylated interferon and ribavirin. He had received a combined liver and kidney transplant for cirrhosis secondary to HCV 1b infection and nephrotic syndrome from cryoglobulinemic glomerulosclerosis and diabetic nephropathy. Six months after transplantation, liver enzymes were increasing with a positive HCV RNA and liver biopsy showing recurrence of chronic hepatitis. Cryoglobulinemia appeared concurrently with burning ulcerations of the lower extremities, with poor tolerance of plasmapheresis. IFN monotherapy had been used but was discontinued at 24 weeks due to lack of response. Once peg-IFN alpha-2b (1 mcg/kg/wk) and ribavirin (400 mg daily) was started, LFTs normalized by the end of the first month and stabilized. HCV-RNA also became undetectable and a sustained virological response was achieved. In addition, leg ulcers rapidly healed by the second month of treatment. Immunosuppression was maintained with tacrolimus. Ribavirin dose adjustment to 200mg/day and erythropoietin were required one month after treatment because of anemia (hemoglobin 102) 1 month after beginning therapy. Hemoglobin, white blood cell count and platelets returned to pretreatment levels after completion of therapy.⁶⁹ Both these case reports involved patients with combined liver/kidney transplants. Although peg-interferon plus/minus ribavirin appeared to be superior to interferon monotherapy it is unclear whether this applies to patients with isolated kidney transplants. Carbognin et al. reported a case of acute renal allograft rejection following peg-IFN-alpha for chronic HCV.⁷⁰ This report features a case of a repeat allograft recipient who presented with neutropenic fevers after 5 months of peg-IFN-alpha therapy, initiated 6 months after the functional loss of his third graft and the re-initiation of hemodialysis. The dose of peg-IFN-alpha 2b used in this patient was 1.5 mcg/kg weekly, since at the time of treatment there were no data to suggest optimal dosing in end-stage renal disease. Currently, the manufacturer recommends a 50% dose reduction for patients on dialysis. Therefore, it is possible that the patient was treated with too high a dose, contributing to graft rejection. In addition, allograft rejection occurred after the patient had been tapered off all his immunosuppressants. Currently, there are limited data to support the use of pegylated-interferon alone or with other antiviral agents in the treatment of chronic HCV in renal transplant recipients.

Currently, treatment of chronic HCV infection after renal

transplantation remains controversial. Not only are interferon and ribavirin less effective in the post-transplant setting, there are significant clinical concerns regarding increased risks of acute renal insufficiency and graft rejection. Emerging evidence supports that these patients should be treated prior to renal transplantation, however, there are few studies on the treatment of HCV post-transplant. Our experience, although anecdotal, is of clinical value, given the paucity of robust clinical trials. Although the risks of allograft rejection and patient morbidity are real, our experience demonstrates that renal transplant recipients with significant target organ damage from HCV can achieve a satisfactory virologic outcome. Both patients and clinicians, however, must accept and prepare for a difficult antiviral treatment course and these patients will require close monitoring.

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