ANNALS of Hepatology

CONCISE REVIEWS

January-March, Vol. 10 No.1, 2011: 5-14

Treatment issues surrounding hepatitis C in renal transplantation: A review

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ABSTRACT

Hepatitis C infection is prevalent in candidates for and recipients of solid organ transplants. In the renal transplant population, HCV infection has been shown to decrease long-term patient and graft survival. The outcomes of HCV in recipients of other solid organ transplants are yet to be established and prospective studies will be needed in the future. In the absence of effective and safe antiviral treatment for HCV infection in renal, heart, and lung transplant recipients, the management of these patients remains a challenge and has led to an increased focus on identifying and treating hepatitis C in patients prior to transplantation. Interferon-based therapy for HCV prior transplantation appears to improve outcomes after transplantation. On the other hand, post-transplant interferon therapy is associated with an increased risk of graft rejection. Given the paucity of information on HCV treatment in solid organ transplant recipients, there is a great need for large-scale, multi-centre randomized controlled trials to determine the optimal approach to HCV infection in this population. This article will summarize the current peer-reviewed literature focusing on the efficacy of amantadine, ribavirin and both standard and pegylated interferon in the treatment of chronic hepatitis C in renal, transplant recipients.

Key words. Hepatitis C, Renal, Transplant, Peg-interferon, Ribavirin.

INTRODUCTION

It is well reported that recipients of extra-hepatic solid organ transplants with chronic hepatitis C (HCV) infection pre-transplant can develop progressive post-transplant liver disease, which is a significant cause of morbidity and mortality. Serum liver biochemical abnormalities are present in 7 to 24 percent of renal transplant (RT) patients, with liver failure determined to be the cause of death in 8 to 28 percent of post-renal transplant recipients.[1,2] The major concern in these transplant recipients is the development of a more rapid and aggressive course of HCV-related infection and liver disease, due to ongoing immunosuppression to prevent graft rejection.[3,4] Immunosuppression post organ transplant has been suggested as a cause of 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. Studies have shown that organ transplant recipients with hepatitis C had significantly worse 10-year graft and patient survival rates. Avoiding excessive immunosuppression is one option to minimize the risk of hepatitis C reactivation. Other treatment options include interferon alpha in combination with ribavirin, which have been approved for both initial treatment and treatment of relapse of chronic hepatitis C, as this has obtained the best results to date.[5-7] The natural history of hepatitis C infection after extra-hepatic solid organ transplants is still incompletely understood. The treatment of chronic hepatitis C in this population remains challenging and is an area that requires ongoing research. This article will summarize the current peer-reviewed literature focusing on the efficacy of amantadine, ribavirin and both standard and pegylated interferon in the treatment of chronic hepatitis C in renal, transplant recipients.

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Manuscript received: November 11, 2010.
Manuscript accepted: November 30, 2010.

HEPATITIS C IN RENAL TRANSPLANT RECIPIENTS

Renal transplant recipients with chronic hepatitis C have been studied more extensively than those who have received heart or lung transplants. The prevalence of chronic hepatitis C virus in dialysis patients has been reported to be as high as 10 to 50% in the US.[8-11] Among the kidney transplant population, the prevalence of chronic hepatitis C infection is high, ranging between 5% to 46%, depending on the countries and/or centers, with the frequency of HCV being much higher among RT patients in 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] The long-term impact of chronic HCV infection on renal transplant is unclear and the data on the outcomes compared with HCV-negative transplant recipients remain conflicting, with most studies showing worse graft and patient survival. Certain factors, such as pre-transplant liver pathology, HCV genotypes, HCV viral load, and type of immunosuppression may influence outcomes of HCV-positive transplant recipients. The impact of immunosuppression on the progression of HCV liver injury and kidney transplant survival remains uncertain. Earlier studies showed a worsening of liver disease in HCV-positive kidney transplant recipients, as immunosuppression may prevent clearance of the virus, leading to increase HCV replication that would eventually cause more liver-related disease.[11,20-22] However, more recent studies have shown relatively slow progression of liver fibrosis in this population.[23,24] Morales *et al.* found that the survival of HCV-positive renal transplant patients was significantly lower than that of HCV-negative patients.[25,26] Post renal transplant, patients with 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.[2,9,27,28] As mentioned above, HCV also has a negative impact on the renal graft survival. It has been reported that development of HCV-related de novo glomerulonephropathy is likely responsible for the decrease in renal allograft survival in HCV positive patients compared to HCV negative patients. Furthermore, chronic HCV infection might also contribute to the development of chronic allograft nephropathy.[25,29,30] Despite the increased liver-related and sepsis-related deaths in HCV-positive renal transplant recipients, renal transplantation does improve overall survival in HCV+ patients on hemodialysis.[31] This is despite the fact that immunosuppressive therapies administered after organ transplantation are responsible for a significant increase in HCV-viremia.[31-33] 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, treatment of chronic hepatitis C infection post renal transplant remains unsatisfactory. Not only are these therapies less effective in the post transplant setting, they are associated with increased risks of acute renal insufficiency and graft rejection. Emerging evidence supports that these patients should be treated prior renal transplantation. The following review summarizes our current understanding of management of HCV infection in this population.

MANAGEMENT OF HEPATITIS C BEFORE RENAL TRANSPLANTATION

The primary goal of treatment of HCV should be eradication of the infection. Secondary aims are prevention of decompensated cirrhosis or hepatocellular carcinoma through sustained viral suppression. Due to the inherent challenges of treating hepatitis C after renal transplantation, many experts have advocated initiating hepatitis C treatment prior to renal transplantation.[34-37] Studies of dialysis patients who were successfully treated before transplantation indicated that HCV eradication is maintained after transplantation. This supports treating dialysis patients before renal transplantation for the prevention of post-transplant complications. The impetus to treat HCV prior to renal transplantation is further supported by concerns that interferon is associated with an increased risk of graft rejection when used post renal transplant. 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.[38] 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%.[39-42] In one study of 78 HCV-positive patients who underwent renal

transplantation, 15 were treated with interferon-alpha for one year prior to transplantation.[42] Of the 15 patients treated with interferon-alpha, 10 (67%) had become HCV-RNA negative by the time of transplantation. Only one (6.7%) patient subsequently developed de novo glomerulonephritis post-transplantation, however this patient was HCV-RNA positive at the time of transplantation. In comparison, it was found that only 29% of the 63 non-interferon-treated allograft recipients were HCV-RNA negative at the time of transplantation, and 12 (19%) developed *de novo* glomerulonephritis (nine with membranoproliferative and three with membranous nephropathy, all 12 patients were HCV-RNA positive at the time of transplantation).[42] Furthermore, interferon-alpha treatment of anti-HCV positive patients undergoing hemodialysis is reported to have a beneficial effect on the course of liver disease following renal transplant, regardless of virological response.[43] At present, data on the relapse rate among renal transplant recipients treated with interferon-alpha for HCV infection prior to transplantation remain 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.[34-36,44]

Peg interferon (peg-IFN) is produced by the addition of polyethylene glycol to interferon. It has reduced volume of distribution and prolonged half –life. Therefore, fluctuations in drug levels are avoided and antiviral efficacy is increased. Unlike standard interferon, pegylated IFN is effective in patients with established cirrhosis. At present, there is little published information on the outcome of treatment with peginterferon 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 (HCV-RNA undetectable at end of therapy) in 83%, sustained virologic response (SVR) (HCV RNA undetectable six months post-therapy) in only 25%, and HCV recurrence in 50%. Tolerance was moderate, with 4/12 (33%) discontinuing treatment due to adverse events, personal decision, or death.[45] Large randomized controlled studies are needed to determine the role of peg-IF treatment in this population. Unlike interferon, ribavirin has usually not been recommended for patients with a creatinine clearance below 50 mL/min as it is renally excreted and the drug and its metabolites are not removed by hemodialysis. Therefore, use of ribavirin in dialysis patients is associated with higher risk of severe hemolytic anemia. However, there is some new evidence supporting the use ribavirin in moderate to severe renal disease as long as there is close therapeutic drug monitoring, dosage adjustment and erythropoietin use should anemia develop.[46,47]

Combination therapy with IFN-alpha plus ribavirin in HCV-infected dialysis patients has been evaluated in several small studies. These demonstrated that, despite the impaired clearance of ribavirin in patients with renal insufficiency, the drug could still be used safely if the dose is adjusted and the hemoglobin levels are closely monitored.[48-50]

MANAGEMENT OF HCV INFECTION AFTER RENAL TRANSPLANTATION

Not all renal transplant recipients who are HCV seropositive after transplant will require antiviral therapy. Only patients with evidence of chronic liver injury should be considered. Antiviral therapy for HCV infection in renal transplant recipients has limited efficacy and can be associated with increased risk of graft rejection.[51-57] However, HCV therapy may need to be considered in the setting of recurrent or progressive HCV-associated glomerulopathy in the transplant kidney, severe cholestatic hepatitis, and advanced histologic stages of liver disease.[58-63] The following summarizes the available evidence on the efficacy and tolerability of different treatment regimens.

AMANTADINE

Amantadine is an oral antiviral agent with immunomodulatory effects with extensive experience in the treatment of influenza. Several small studies have reported that oral amantadine can improve aminotransferase levels in patients with hepatitis C.[64,65] In addition, it had been suggested that amantadine may potentiate the antiviral effects of the combined regimen of interferon-alpha plus ribavirin in patients with chronic hepatitis C.[66] A pilot study of nine HCV-positive renal transplant recipients by Rostaing, *et al.* reported that amantadine was associated with a significant decrease in both ALT and AST levels, which fell within the normal ranges after therapy. However, there were no significant changes in GGT levels or in HCV RNA concentra-

tion. These authors further concluded that the clinical, renal and hematologic tolerance was found to be acceptable.[67] Similarly, Kamar, *et al.* found that six months of amantadine (200 mg per day) was well tolerated among HCV-positive renal transplant recipients with some beneficial effect on serum aminotransferases, but not on HCV RNA levels or liver histology.[68] A small controlled study by Calanca, *et al.* in 2007 compared ribavirin monotherapy with combination therapy including amantadine. The authors reported no significant changes in transaminase levels after treatment in both groups, and HCV replication was not significantly affected by either treatment regimen. Levels of proteinuria were not affected in either group. The addition of amantadine to ribavirin did not appear to be superior to ribavirin monotherapy in renal transplant patients with chronic HCV infection. Moreover, the poor tolerance of both ribavirin and amantadine in patients with impaired renal function resulted in increase drop-outs and sub-therapeutic drug dosing.[69]

Overall, the limited available data suggests that amantadine appears to be safe and well tolerated in HCV positive renal transplant patients; however, it lacks efficacy. Amantadine improves liver enzymes but has not been shown to reduce HCV viremia or improve liver histology. A significant role for amantadine in treatment of HCV in renal transplant recipients is unlikely.

RIBAVIRIN MONOTHERAPY

Ribavirin (1-β-Dribofuranosyl-1,2,4-triazole-3-carboxyamide) is a synthetic guanoside analog that inhibits viral RNA-dependent RNA polymerase by depleting intracellular guanosine pools and interfering with the capping of RNA. Ribavirin monotherapy may decrease the HCV-related liver injuries by its immune modulatory properties, even in absence of an antiviral effect.[70] Ribavirin clearance is reduced in patients with renal insufficiency and the drug and its metabolites are not removed by hemodialysis. Therefore, ribavirin has traditionally been not recommended for patients with a creatinine clearance below 50 mL/min, due to the risk of severe hemolytic anemia. However, newer evidence does support its use in moderate to severe renal disease with close therapeutic drug monitoring, adjusted ribavirin dosing in conjunction with erythropoietin use for development of anemia.[46,47] Experience with ribavirin monotherapy in transplant recipients has largely been after liver transplantation, with controversial results reported regarding the effects of ribavirin on liver histology.[71-73] In the liver transplant literature, ribavirin monotherapy for chronic HCV infection after liver transplantation results in decrease in aminotransferase levels, with possible liver histology improvement.[71] Furthermore, Pham et al. showed that ribavirin was able to induce complete remission of de novo HCV-related glomerulonephritis with a significant reduction in serum creatinine in liver transplant patients.[72] However, there are limited studies supporting the efficacy of ribavirin monotherapy in renal transplant patients for HCV-related liver disease. In 1997, Garnier *et al.* treated seven patients with stable kidney graft function who were HCV RNA positive; five of them had chronic hepatitis on liver biopsy. They were treated with ribavirin monotherapy 400-800 mg/day for 6 months. On treatment, four patients (57%) had a biochemical response, but HCV RNA was undetectable in only two (29%). Although ribavirin monotherapy failed to clear HCV RNA in renal transplant recipients, at least half of the patients (57%) had a decrease in HCV RNA viral load by 70 to 82%, and the treatment was not associated with any significant graft dysfunction. No information on outcome was provided after 6-month of ribavirin monotherapy. The only significant side effect was the occurrence of transient mild hemolytic anemia, which resolved after therapy was tapered.[74]

In 2003, Kamar, *et al.* evaluated the biochemical, virological, histological efficacies, as well as the safety of one year ribavirin monotherapy in renal transplant patients with HCV. Sixteen patients in the study group (32 patients in control) were started on ribavirin 1000 mg daily, with further doses adjustment based on hemoglobin levels. Ribavirin monotherapy was associated with a significant decrease in AST, ALT and gamma glutamyl transpeptidase levels. Serum creatinine decreased as well, but without significant reduction in HCV viremia. On liver biopsy, there was a significant progression in liver fibrosis with no improvement in inflammation scores. In terms of side effects, there was a significant decrease in hemoglobin levels, despite the use of erythropoietin. Three patients (19%) required discontinuation of ribavirin therapy. The conclusion of this study was that ribavirin monotherapy in RT patients with HCV has no impact upon liver histology, although it improves liver enzymes.[75] In 2004, Fontaine *et al.* studied thirteen kidney transplant recipients with detectable HCV RNA and severe histologic injury on liver biopsy who were treated with ribavirin for a median duration of 22 months (with no control group). Although no virological response

was found, there was a significant improvement in biochemical parameters and the fibrosis score was improved in five of thirteen (38%) patients. In addition, no severe adverse effects were seen and erythropoietin treatment was required for only one patient with anemia secondary to ribavirin.[76] Similar findings were reported in subsequent studies by Karaca *et al.* and Sharma, *et al.* Renal transplant recipients with detectable HCV RNA and persistently elevated aminotransferases were treated with ribavirin monotherapy. Although a majority of the patients showed biochemical response, none demonstrated virological response and liver histology was not evaluated in these studies. Hemolytic anemia remained as a significant side effect.[58,77]

Based on these results, ribavirin monotherapy appeared to have some biochemical efficacy in renal transplant recipients with HCV. The efficacy on liver histology remains controversial and further studies with larger cohorts are still needed to assess the impact of ribavirin on liver histopathology.[24,75,76,78] In addition, ribavirin monotherapy might improve the level of proteinuria in renal transplant recipients with HCV-related *de novo* glomerulopathy; however, only a small number of patients were assessed in these studies.[75] Because of its significant side effect (i.e. hemolytic anemia) and limited efficacy, ribavirin monotherapy is currently not recommended in the management of HCV disease in kidney transplant recipients.

INTERFERON EFFICACY AND GRAFT DYSFUNCTION

Currently, the combination of pegylated-interferon-alpha and ribavirin is the mainstay treatment for hepatitis C in patients with normal renal function.[6,7] In the HCV-positive renal transplant population, this treatment may be associated with addition complications. Since these patients receive maintenance immunosuppression that might lead to increase HCV RNA concentration in the serum, these patients have a significantly higher HCV viremia than pre-transplant values.[1,79] The use of interferon-alpha after renal transplantation in fact has been complicated by the onset of acute rejection, thus limiting its use in this population. The mechanism of IFN-induced rejection after RT remains unknown. *In vitro* observations have reported that IFN could produce cell-surface expression of HLA antigens with induction of cytokine gene expression and subsequent stimulation of antibody production. Furthermore, IFN may enhance donor specific antibodies production, inhibition of prostaglandin synthesis leading to immunologically mediated nephropathy, or stimulation of antibody production by B cells. The use of IFN-alpha as 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.[80,81] Importantly, 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.[82]

Over the last decade, IFN monotherapy has been used to treat HCV-positive RT recipients. In these studies, about half of the patients showed improvement in aminotransferases with interferon therapy and about 25 % lost HCV RNA, but only a minority with a sustained virological response.[59,60,83-85] A concerning feature was that acute cellular or humoral rejection appeared to be more frequent among alpha IFN treated patients, and in many series instances of renal failure and graft loss (despite aggressive immunosuppressive therapy) were common.[52-54,57] In 2006, Fabrizi, *et al.* performed a meta analysis of 12 trials (102 patients) to evaluate the safety and efficacy of interferon in renal transplant patients with hepatitis C. The primary outcome of interest was sustained virological response (SVR) and/or drop out rate. SVR was a measure of efficacy, defined as disappearance of HCV viremia (HCV-RNA) by PCR at least 6 months after completion of therapy. An additional outcome was the sustained biochemical response (SBR), defined as the normalization of ALT levels at least 6 months after the completion of therapy.[55] This study found that the mean overall estimate for SVR in HCV-positive RT recipients treated with IFN monotherapy was 12.0%; this response was similar to that typically reported in non-uremic patients with chronic hepatitis C. However, this meta-analysis also demonstrated that graft dysfunction occurred in nearly one-third of RT recipients and they were frequently irreversible and steroid-resistant. The association of acute renal failure and graft rejection in renal transplant recipients treated with interferon for chronic hepatitis C documented by many studies has led to the recommendation that patients with a renal transplant should not be given interferon alpha.[5,55,67,86]

Therefore, the limited efficacy of IFN-alpha, together with its high cost, risk of acute rejection and

side-effects have diminished the enthusiasm for its use in renal transplant recipients with chronic HCV infection. 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.[25,87-89] 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.

INTERFERON AND RIBAVIRIN COMBINATION THERAPY

There has been limited experience with the use of interferon and ribavirin combination in the treatment of chronic hepatitis C in renal transplant (RT) recipients. Currently, in the non-transplant setting, peginterferon and ribavirin (see next section) is the only licensed therapy and standard of care. The addition of ribavirin to peg-interferon(IFN)-alpha is superior to peg-IFN monotherapy, with a higher sustained virological response rate (SVR), from 29% (peg-IFN monotherapy) to 56% (peg-IFN and RBV).[6,7] Some investigators have suggested that the addition of ribavirin to interferon in the treatment of transplant recipients has the potential of increasing the rates of sustained virological response, while also protecting against allograft rejection, as postulated in liver transplant recipients.[90] Ribavirin is known to exert an inhibitory effect on pro-inflammatory Th2 cytokine responses that might partially ameliorate the detrimental immunological actions of interferon on graft function.[60,91] Recently, there have been a few case reports reporting successful treatment of chronic hepatitis C in renal transplant recipients with interferon and ribavirin.[60-63,85,92] In one report, Zeman, *et al.* presented a HCV-positive renal transplant recipient with deteriorating renal function and proteinuria secondary to recurrent membranoproliferative glomerulonephropathy. This patient was successfully treated with a post-transplant course of interferon-alpha and ribavirin combination therapy. Immunosuppression consisted of tacrolimus, mycophenolate and prednisone. Despite HCV clearance, which was sustained over two years, symptomatic cryoglobulinemia continued.[61] Based on these case studies, combination therapy of interferon and ribavirin might be a treatment option for carefully selected HCV positive renal transplant recipients, provided that adequate immunosuppression is maintained and they are carefully monitored.[60,61]

In 2003, Tang, *et al.* reported on the use of IFN-alpha plus ribavirin to treat four HCV positive renal-transplant patients.[60] These four patients developed sub-acute HCV infections in the first four months following renal transplantation. The disease was so severe that they treated these patients with 48 weeks of IFN-alpha-2b plus ribavirin. Three patients (75%) showed clearance of the HCV virus without any change in their renal function, with sustained virological and biochemical remission (SVR and SBR). The median time from initiation of treatment to ALT normalization was 8 weeks. The fourth patient was a non-responder infected with genotype 1b, with dose-dependent hemolysis as the most frequent side-effect, requiring ribavirin dosing adjustment or temporary discontinuation. None of these patients developed allograft dysfunction. Based on this study, the use of interferon and ribavirin could be considered in selected renal transplant recipients with severe acute hepatitis C infection.

In 2004, Shu, *et al.* reported their success in treating 11 renal transplant recipients with active hepatitis C with "ultra-low dose" interferon-alpha (1 x 10 units subcutaneously three times/week) and ribavirin (600 mg/day). After 48 weeks of treatment, all patients except one (91%) had a biochemical response, with normalization of serum ALT level at a median of 1.1 months post-treatment. Five patients (45%) were HCV RNA negative at the end of treatment, while three (27%) had a sustained virological response. No histopathologic data was reported, as no liver biopsies were taken. Only one patient (9%) terminated the treatment due to acute graft failure, who was subsequently treated using methylprednisolone with restoration of graft function. The authors concluded that ultra-low dose interferon-alpha and ribavirin was relatively safe for the treatment of chronic HCV infection in renal transplant recipients, with a significant portion of patients achieving a sustained biochemical and virological response.[59] In 2006, Sharma, *et al.* administered interferon and ribavirin combination therapy to six renal transplant recipients with markedly elevated liver enzymes secondary to underlying hepatitis C. The mean ALT levels decreased significantly (from 280.2 ± 114.9 IU/L at baseline to 71 ± IU/L at end of therapy; $p < 0.05$). Two patients had sustained remission (33%) on therapy (persistently negative HCV-RNA), and two patients relapsed after initial remission. In total, four patients developed graft dysfunction (66%), but only two (33%) required their therapy discontinued. This study showed that although IFN therapy in combination with ribavirin

can be effective in sustaining virological remission in one-third of patients, it is poorly tolerated, resulting in graft dysfunction in significant numbers of patients. In addition, relapse can occur after discontinuation of treatment.[58]

PEGYLATED INTERFERON

Pegylation of interferon-alpha (peginterferon, pegIFN) is produced by the addition of multiple polyethylene glycol moieties to a parent drug molecule. This larger pegylated interferon molecule has a reduced volume of distribution and prolonged half-life, enabling once weekly administration. Peginterferon has fewer side effects and better antiviral efficacy. Furthermore, viral clearance occurs more rapidly than the standard interferon therapy in most responders. In patients without end-stage renal disease, pegIFN has a sustained response rate of 39%, more than double the rate of standard IFN. Unlike regular IFN, pegIFN does not undergo extensive renal clearance and should be safe in dialysis patients. Although prior studies have reported a high incidence of graft rejection in HCV-positive renal transplant recipients treated with non-pegylated interferon, it is uncertain whether this holds true for pegylated interferon. Antigenicity and immunogenicity may be decreased secondary to the "water-cloud" effect of pegylation.[62,63,93] However, only limited studies have evaluated the use of pegIFN for the renal transplant population.

One study switched three patients from IFN to peg IFN during treatment, without development of renal allograft rejection.[54] This retrospective study by Baid, *et al.* identified twelve HCV positive renal transplant recipients who had been treated with interferon (1.5 to 3 million units three times weekly) plus/minus ribavirin (200 to 800 mg/day) for biopsy proved chronic hepatitis C. In three patients, interferon was subsequently changed to pegIFN at a dose of 1-1.5 µg/kg once weekly. These patients who were switched to pegIFN were also treated with ribavirin, and did not develop any graft rejection. However, it is unclear from the study at which point the patients were switched to pegIFN, and how long this drug was continued. 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 pegylated interferon-2a 180 µg/week and ribavirin 1,200 mg/day for 48 weeks. Immunosuppression was maintained with tacrolimus and prednisone. No adverse effects were reported and renal function remained normal. At three months, the aminotransferases normalized and HCV RNA was undetectable. The biochemical and virological response were sustained at the end of treatment and six months afterwards. The patient continued to have normal liver tests and serum creatinine and remained HCV RNA negative eighteen months after treatment.[63] 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 underwent 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. Unfortunately, plasmapheresis was poorly tolerated. IFN monotherapy had been used but was discontinued at 24 weeks due to lack of response. Once peginterferon alpha-2b (1 µg/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 200 mg/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.[62] 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 pegIFN-alpha for chronic HCV.[94] This report features the case of a repeat allograft recipient who presented with neutropenic fevers after 5 months of peginterferon-alpha therapy, initiated 6 months after the functional loss of his third graft and the re-initiation of hemodialysis. The dose of Peginterferon-alpha 2b used in this patient was 1.5 µg/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 reduc-

tion for patients on dialysis. Therefore, it is possible that the patient was treated with too high a dose, contributing to graft rejection. It is also possible that allograft rejection in this case was unrelated to interferon use, although other potential factors were not identified. 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.

SUMMARY

Despite the wide-spread use of interferon-based therapy in combination with ribavirin for the treatment of chronic hepatitis C in the non-transplant population, supported by robust phase 2, 3 and post-marketing clinical studies, there is a marked scarcity of both clinical studies and clinical experience in the pre-and post-renal transplant setting. The lack of robust clinical studies makes an evidence-based approach to treating these patients difficult. Based on our review, it may be reasonable to attempt to clear HCV pre-transplant while these patients are on dialysis. The inability to use ribavirin in this setting, however, handicaps the likelihood of a sustained virologic response. In the post transplant setting, it is clear that amantadine and ribavirin monotherapy are not clinically efficacious and their use most likely cannot be recommended. The use of interferon alpha post-renal transplant is associated with a very real risk of precipitating acute graft rejection. The risk of graft rejection with peg-interferon in combination with ribavirin, however, is not clear and it may be that select patients who are monitored vigilantly may benefit. The likelihood of a sustained virologic response in this setting is still disappointing. Whether the new protease and polymerase inhibitor agents that are currently undergoing phase 2 and 3 studies, in combination with peg-interferon and ribavirin, will be studied in the post-transplant setting any time in the near future remains to be seen.

ABBREVIATIONS

- **HCV:** Hepatitis C virus.
- **peg-IFN:** Peg-interferon
- **SVR:** Sustained virologic response.
- **RT:** Renal transplant.
- **HT:** Heart transplant.
- **LT:** Lung transplant
- **HBV:** Hepatitis B virus.
- **HCV-RNA:** Hepatitis C ribonucleic acid.
- **ALT:** Alanine Transaminase.
- **AST:** Aspartate aminotransferase.
- **GGT:** Gamma-glutamyl transpeptidase.
- **ETR:** End of treatment response.

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