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Review

Management of HCV Infection and Liver Transplantation

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A major challenge facing liver transplant recipients and their physicians is recurrence of hepatitis C virus infection following otherwise technically successful liver transplantation. Recurrent infection leads to diminished graft and patient survival. Although a number or predictors of severe recurrence have been identified, no definitive strategy has been developed to prevent recurrence. Generally the tempo of hepatitis C recurrence is gauged by serial liver biopsies with the decision to intervene with antiviral therapy based on local philosophy and expertise. Treating hepatitis C in this population has a number of major challenges including diminished patient tolerance for side-effects as well as managing the patient's immunesuppression. However sustained viral responses are possible with the potential to reduce the impact of recurrent hepatitis on the graft. However recurrent hepatitis C virus infection will remain the most frequent form of recurrent disease in liver transplant programs for the foreseeable future.

Key words: recurrent hepatitis C, liver transplantation, antiviral therapy

1. Treatment of HCV in the Liver Transplant Population

Currently there are approximately 17,000 patients on liver transplant waiting lists throughout the U.S. with approximately 5,000 liver transplants performed annually [1,2]. Because of a critical shortage of donor livers, 10%-12% of potential recipients die before they are transplanted. About 40% of liver transplants are performed in patients having HCV and this number is expected to significantly rise during the next decade, especially with burgeoning rates of hepatocellular carcinoma [2,3]. Traditionally, cirrhotic patients were not considered as candidates for interferon therapy as it was believed that in the setting of hepatic encephalopathy, ascites and protein malnutrition they would not tolerate therapy and also that their liver disease would potentially decompensate with treatment. However, improved response rates using the combination of pegylated interferon and ribavirin, greater experience in using hematopoietic growth factor and the need to proactively treat patients on the liver transplant waiting list have all stimulated interest in treating HCV patients with cirrhosis [1,4,5]. For the foreseeable future most HCV infected transplant candidates will be viremic at the time of transplant and will therefore remain at risk for recurrent infection. The therapy of HCV post-OLT has evolved to the point where most centers base treatment decisions on the tempo of HCV recurrence on serial liver biopsies although more and larger scale studies are needed in this population.

2. Hepatitis C Post-Liver Transplantation

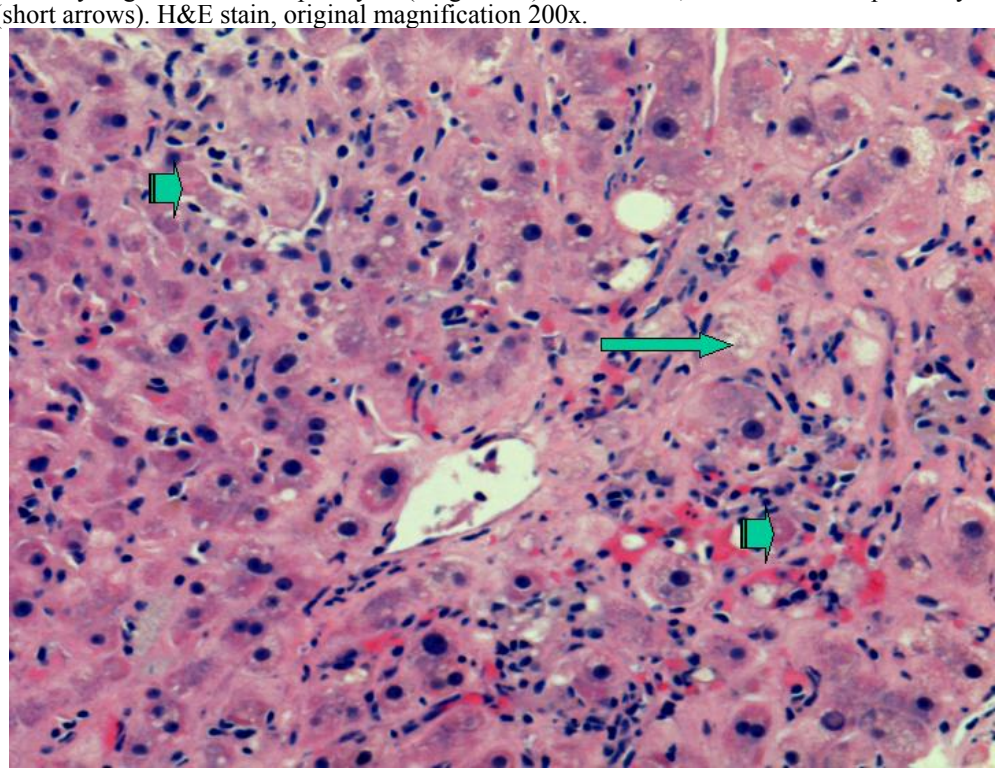
In liver transplant (LT) recipients, persistence of hepatitis C (HCV) infection in viremic recipients almost always leads to graft reinfection. In fact, serum viral titers may reach pre-transplant levels within the first few days post-operatively. Serum levels of HCV RNA peak 1-3 months post-transplant, reaching titers many fold higher than pre-transplant levels [4,6]. Furthermore, histological evidence of HCV recurrence occurs in over 90% of patients within 5 years of the transplant and has a variable clinical course [1,6]. Histological progression of HCV is accelerated after LT and can result in the fairly rapid development of graft failure and cirrhosis [7,8,9]. Several studies have shown that as many as 20% of HCV patients undergoing liver transplant may develop cirrhosis within 5 years, with almost 50% developing cirrhosis within a decade. Once patients develop cirrhosis from recurrent HCV, they are at risk for the same complications as other patients including variceal bleeding, ascites and hepatocellular carcinoma. Berenguer and colleagues observed rapid hepatic decompensation in LT recipients with graft cirrhosis due to recurrent HCV [1,4,10].

Recent studies looking at large numbers of patients with adequate long-term follow-up have confirmed that patients with HCV undergoing liver transplantation have increased morbidity and mortality and have lower 5 and 10 year survival rates when compared to patients undergoing liver transplantation for other etiologies of cirrhosis [1,8,9]. HCV is the most frequent indication for LT in the United States and in Europe. By the year 2020 the proportion of untreated HCV patients developing cirrhosis is expected to increase by 30%, the number of cirrhotic patients with HCV to increase by 100%, and the number of HCV cirrhotic patients developing hepatocellular carcinoma by 80% [2]. With the anticipated increase in patients requiring LT for HCV related liver disease, development of effective strategies to reduce graft failure due to HCV recurrence is essential.

A number of reports have described accelerated fibrosis progression post-liver transplantation and this may in part be due to the age of the donor liver allograft [10]. The median rate of fibrosis progression is between 0.3 and 0.6 stage per year post-transplant compared to 0.1 to 0.2 stage per year in immunocompetent HCV patients. Various risk factors for poor outcomes post-LT for HCV

have been described. Berenguer et al have shown that the use of liver allografts from deceased donors older than age 60 is associated with a more severe recurrence of HCV as well as a more rapid progression to cirrhosis when compared to LT recipients receiving allografts from younger donors [10]. Once patients develop cirrhosis post-transplant, the 1 and 3 year actuarial risks of decompensation are 42% and 62%, respectively, vs. less than 5% by 1 year and less than 20% by 5 years in immunocompetent patients with chronic HCV infection [1,4,5]. A subset of patients develop a severe cholestatic form of HCV that rapidly progresses to graft failure, similar to the fibrosing cholestatic hepatitis that originally described in patients with recurrent hepatitis B post-transplant. Characteristically, there is a very high HCV serum RNA level, profound hyperbilirubinemia and high levels of alkaline phosphatase and gamma-glutamyl transferase, and liver biopsy reveals feathery degeneration predominantly in the perivenular area (Figure 1), portal tracts showing chronic inflammation ranging from mild-severe with occasional lymphoid aggregates (Figure 2) [4,11]. Actively proliferating bile ductiles are often seen. Risk factors for severe recurrent HCV include advanced donor age, HCV genotype 1, high HCV RNA levels before and after transplant, early histological recurrence of HCV, concomitant cytomegaloviral infection, the use of T lymphocyte-depleting immunosuppressive agents such as OKT3, and treatment of presumed acute cellular rejection with pulse corticosteroids. Data are conflicting as to whether recipient age, warm or cold ischemia times, gender, HLA mismatch, ethnicity or pre-transplant severity of illness influence the rate of recurrent HCV and its severity [1,4,5,12,13,14].

Figure 1. Liver needle biopsy showing severe recurrent hepatitis C, cholestatic type. This photomicrograph shows centrilobular cholestasis causing feathery degeneration of hepatocytes (long arrow). In addition, there are foci of parenchymal necrosis including acidophilic bodies (short arrows). H&E stain, original magnification 200x.



Excessive immunosuppression appears to have a deleterious effect on HCV recurrence post-liver transplant [1,15]. High dose maintenance corticosteroid therapy for the prevention of acute cellular rejection has been associated with decreased patient and graft survival in HCV-infected transplant recipients. With regard the use of cyclosporine- or tacrolimus-based immunosuppression, no significant differences in survival or in frequency/severity of HCV recurrence have been found. The impact, if any, of azathioprine, mycophenolate mofetil and sirolimus on HCV natural history post-liver transplant remain unclear [1,5]. It can be extremely difficult at times to differentiate between acute cellular rejection and recurrent HCV histologically even for experienced liver pathologists because most patients will have some baseline features of hepatitis on the biopsy, as well as varying degrees of the histological features that define allograft rejection such as interface inflammatory changes and bile duct damage [4,16]. Thus, repeated liver biopsies may be required when there is an elevation in liver chemistry tests to more reliably diagnose HCV recurrence. The optimal strategy in managing immunosuppression post-liver transplant in the HCV patient thus appears to be achieving a balance between the prevention of rejection while minimizing the potential deleterious effects of immunosuppression on recurrent HCV [1,4]. However, this is extremely difficult to achieve in most patients.

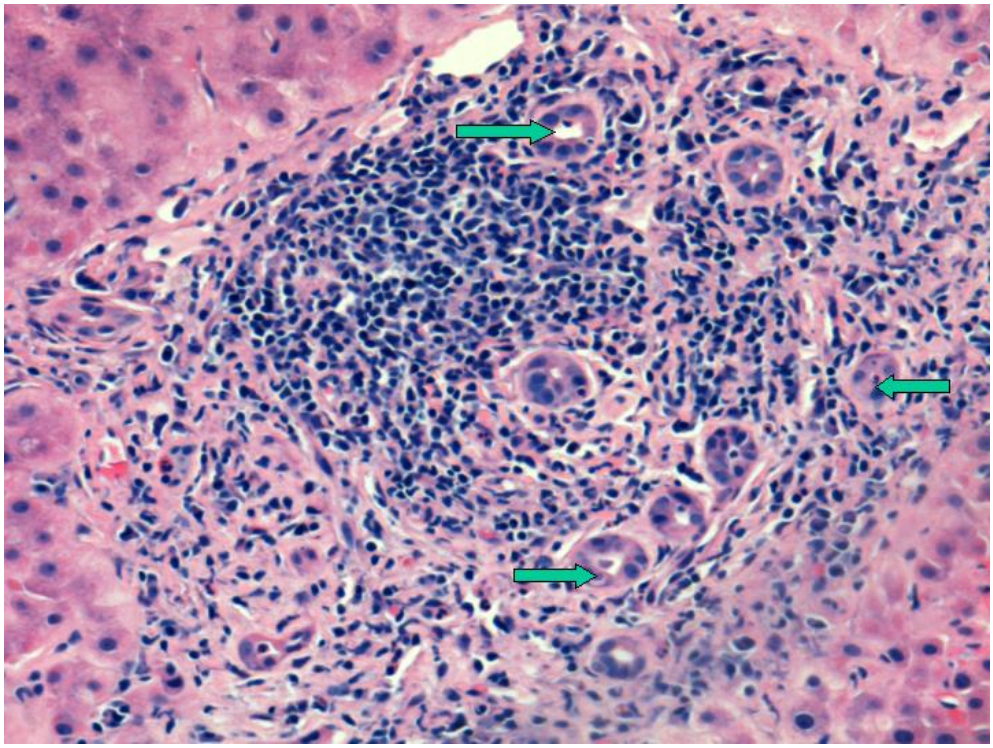
In the post-liver transplant setting the differential diagnosis of elevated liver chemistry tests is broad and includes acute cellular or chronic ductopenic rejection, bacterial or viral (CMV most frequently) infection, drug hepatotoxicity, ischemia or viral hepatitis. Approximately 20-30% of patients with recurrent HCV may have normal aminotransferases; it is for this reason that some centers favor protocol liver biopsies in HCV patients post-liver transplantation. Histologically, acute HCV recurrence is characterized by lobular infiltrates with varying degrees of hepatocyte necrosis

which may evolve over time to a chronic hepatitis with significant portal and lobular infiltrates and hepatocyte necrosis, as well as portal-to-portal bridging fibrosis.

Early in the era of adult-to-adult live donor liver transplantation, preliminary reports suggested that patients undergoing this partial liver transplant had more severe HCV recurrence [1,4]. Although a well designed study from Europe did show a higher rate of graft failure in HCV recipients of live donor liver transplantation as compared to HCV(+) recipients of deceased donor livers, several more recent studies including one utilizing protocol liver biopsies and another an analysis of the UNOS database of a large number of patients, have not shown worse graft or patient survival in patients undergoing live donor liver transplantation [17,18].

Several studies have shown that patients undergoing retransplantation for recurrent HCV experience significant morbidity and mortality. Although there is decreased patient and graft survival after retransplantation in general, it appears that results are even poorer for patients when the etiology of graft failure is recurrent HCV. In a large single center experience Roayaie et al noted a median survival of 12.9 months in 42 patients undergoing retransplantation because of graft failure due to recurrent HCV; 20 of the patients died within 6 months, almost all from sepsis. The presence of renal dysfunction, thrombocytopenia and coagulopathy were negative prognostic variables for survival [19]. Whether to retransplant patients with recurrent HCV is a difficult decision because of the decreased patient and graft survival that occurs after retransplantation in an era in which there are frequent deaths on the liver transplant waiting list and a finite number of donor livers. Whether a patient with HCV recurrence was unable to tolerate interferon treatment or was a virological non-responder must be considered in the decision making process when retransplantation becomes necessary, although data on this point is needed.

Figure 2. Same case as above showing a portal area with a dense lymphoid aggregate typically seen in chronic hepatitis C. Arrows point to proliferating bile ductules (ductular reaction). The bile duct is intact albeit slightly damaged. H&E stain, original magnification 200x.



Currently, interferon-based therapies are the only effective treatment for HCV post-liver transplantation. Treatment early after liver transplant is difficult because of the patient's often poor performance status, their increased susceptibility to infection and rejection, and the presence of anemia and renal dysfunction that lessen the tolerability of interferon and ribavirin [1,4,5,20,21]. It is for these reasons, in addition to the fact that an undetectable or low viral load at the time of transplant is associated with less severe HCV recurrence, that pre-transplant antiviral therapy is frequently attempted [22]. To date, preemptive treatment to prevent HCV recurrence post-liver transplantation has not been shown to be highly effective; Chalasani et al recently demonstrated less than a 10% sustained virological response rate in patients receiving 48 weeks of peginterferon alfa-2a monotherapy [23]. The First ILTS Expert Panel Consensus Conference concluded that prophylactic and preemptive antiviral interferon-based therapy should only be used in specific circumstances, such as for non-HCV patients receiving HCV (+) donor allografts [4]. The response rate with standard interferon monotherapy and standard interferon in combination with ribavirin to treat post-liver transplant HCV has generally been associated with modest response rates. However, small single center trials in patients treating established recurrent HCV using the combination of pegylated interferon alpha-2b and ribavirin have resulted in end-of-treatment and sustained virological response rates ranging from 27-64% and 0-36%, respectively [24,25]. Treatment of recurrent HCV is limited by decreased patient tolerability necessitating frequent dose adjustment and the inability to achieve optimal dosing. Approximately 30% of patients will discontinue therapy. Often the only way of maintaining

the blood counts is to aggressively use hematopoietic growth factors. The often poor tolerability of this population to any interferon and ribavirin regimen reflects a number of factors including concomitant immunosuppressive agents and associated renal dysfunction. An important concern has been whether interferon can induce graft rejection as has been reported in renal transplant recipients. Chalasani et al in their controlled clinical trial did not observe any increase in rejection rates in liver transplant recipients treated with pegylated alfa-2a [23]. Stravitz et al have described profound graft dysfunction following successful interferon clearance of HCV RNA with a picture suggestive of chronic ductopenic rejection [26]. One explanation may be that following clearance of HCV infection hepatocellular function improves and in turn leads to rejection. There have been increasing reports of pegylated interferon and ribavirin therapy possibly increasing the rates of both acute cellular and chronic ductopenic rejection [23]. Castells et al in a recent report described an SVR of 34% in genotype 1patients treated a mean of 3.4 months following OLT suggesting a role for therapy early in the course of HCV. Importantly a predictor of interferon response was an absence of treatment for acute rejection [28].

At our institution, patients with HCV undergo protocol liver biopsies every 6 months, and interferon and ribavirin are started only in the presence of progressive fibrosis. Firpi and colleagues from the University of Florida have described an important prognostic role for the severity of liver biopsy findings 1 year post-OLT [29]. We utilize an escalating dose regimen of both pegylated interferon and ribavirin, and we aggressively utilize hematopoietic growth factors early in treatment to help stave off the need to discontinue therapy. Although thrombocytopenia may persist after portal hypertension resolves post-transplant, it is rarely a limiting factor to pegylated interferon use. We treat patients for 12 months and check monthly laboratory testing to exclude acute and chronic rejection.

The worsening organ donor shortage has necessitated the use of HCV (+) allografts in recipients with HCV. It appears that short-term patient and graft survival are similar compared with a cohort of HCV (+) recipients receiving HCV (-) allografts. A HCV (+) patient who is HCV RNA (-) should not receive a HCV (+) allograft. As it appears that the donor allograft genotype predominates after transplantation, our center's practice is to not use HCV (+) donors for patients with genotype 2 and 3 [4,5]. It is prudent to avoid the use of HCV (+) livers from older donors or those having any histological damage.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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