

Preemptive Treatment of Hepatitis C After Liver Transplantation

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Currently, more than 30% of patients receiving liver transplants are infected with the hepatitis C virus (HCV) in the United States. Thus, hepatitis C has become the leading indication for orthotopic liver transplantation. Data from the Organ Procurement and Transplantation Network Web site (<http://www.optn.org/data>) reveal that more than 17,000 individuals are awaiting liver transplants and approximately 3,000 transplantations were performed in 2005, underscoring the fact that the current demand for transplants of this organ clearly outweighs the supply.

After transplantation for end-stage liver disease secondary to HCV, recurrence of infection is universal, with the majority of patients developing histologic hepatitis. Approximately 10–30% of these patients progress to cirrhosis after a median of only 5 years after undergoing transplantation¹; that is, progression of hepatitis C is accelerated in immunocompromised liver transplant recipients compared with immunocompetent patients. Recent data also suggest that HCV-related disease progression is faster in patients who have undergone transplantation in recent years compared with those who underwent transplantation earlier. Unfortunately, predictors of severe recurrence remain poorly defined. Taken together, effective therapy to optimize outcomes in HCV-infected patients after liver transplantation is imperative.

One approach to combating HCV fibrosis progression posttransplantation is to proceed with therapy only after significant histologic recurrence. At many centers significant recurrence is monitored through the use of protocol biopsies (ie, biopsies done at defined intervals

after transplantation); thus, with this approach, treatment is not initiated until disease has already progressed. An alternative approach is to initiate therapy before development of significant histologic injury, also known as preemptive therapy. The latter approach may be the better one for several reasons.

Firstly, there already exists a precedent for success with preemptive therapy for viral hepatitis following liver transplantation. Until recently, liver transplantation was associated with a 75% risk of recurrence of hepatitis B and a 3-year survival rate of approximately 60%, with the greatest risk being among those with active viral replication prior to transplantation.² With the advent of the use of hepatitis B immune globulin and, more recently, nucleoside and nucleotide analogs after transplant, graft and patient survival have improved tremendously.³ As a result, transplantation for end-stage liver disease secondary to this virus is no longer controversial. Thus, it seems reasonable to suggest that such a strategy for treating HCV may be of benefit.

Secondly, following liver transplantation the allograft is acutely infected with HCV. In the nontransplant setting, treatment of acute HCV infection has resulted in sustained virologic response rates of greater than 90%.⁴ By contrast, the treatment of chronic, or “established,” hepatitis C results in a sustained virologic response rate of less than 50%.^{5,6} Although a higher viral titer is noted in the immunosuppressed setting, it remains reasonable to hypothesize that hepatitis C recurrence may be most amenable to therapy during acute infection.

A further rationale for preemptive therapy is that interferon and ribavirin have been shown to be more effective immediately following transplantation than in the treatment of more advanced recurrent HCV.⁷ Although there are case reports of biochemical and partial virologic responses to treatment in transplant recipients with cholestasis, initiation of combination therapy in patients who are already cholestatic is generally unsuccessful.^{7,8}

One may argue that preemptive therapy would be difficult to tolerate following transplantation and is therefore

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a poor strategy for management of hepatitis C recurrence. Anemia, leukopenia, prolonged preoperative hospitalization, and postoperative complications all contribute to the potential challenges of this approach. However, with the advent of growth factors, better management of side effects in general, and the use of interferon dose-escalation strategies (now used in patients with cirrhosis, another challenging group of patients with similar issues), the use of preemptive therapy has become a reasonable approach to consider.

The strategy suggested by the International Liver Transplantation Society for the management of hepatitis C is to monitor patients for significant histologic recurrence and to initiate therapy only if this occurs.⁹ However, as outlined above, posttransplant HCV infection may be most amenable to therapy when initiated early in the posttransplant course. Data supporting this approach are limited to date due to the small numbers of patients studied and the use of uncontrolled study design,¹⁰ making it difficult to draw conclusions on efficacy and tolerability. The tolerability of preemptive therapy should improve as the use of growth factors for neutropenia and hemolytic anemia become more widespread, and as treatments for other side effects such as depression improve. Therefore, preemptive therapy should continue to be considered a potentially viable approach to the management of hepatitis C recurrence following liver transplantation. The safety and efficacy of antiviral therapy initiated preemptively versus upon histologic recurrence warrants a definitive comparison and is the subject of ongoing research.

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CON

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The management of hepatitis C following liver transplantation is one of the most ubiquitous, difficult, and controversial issues in liver disease. Currently, hepatitis C is the most common indication for liver transplantation in the United States, with 30% or more of liver transplant recipients infected with the virus.¹ Recurrence is essentially universal in all patients after transplantation and HCV-infected patients have a 23% higher posttransplantation mortality rate compared to non-HCV patients who undergo liver transplantation, largely due to graft loss from recurrent disease.² There are 3 basic approaches to managing hepatitis C after liver transplantation. Perhaps the most common approach is to perform reflexive liver biopsies in patients with elevated liver function tests and a yearly protocol biopsy in all patients to evaluate for progressive fibrosis. Patients with stage 2 (of 4) or higher hepatitis C may be initiated on treatment with pegylated interferon and ribavirin. Some centers have found that the side effects of interferon therapy may exceed the clinical and histologic benefits.³ In this case, treatment may be reserved for patients with severe recurrence. Finally, a few centers administer preemptive therapy in which all patients are treated with interferon and ribavirin immediately after transplantation, regardless of histologic or clinical indicators for therapy.

There are several reasons why preemptive therapy after transplantation is not recommended. First, interferon therapy is not particularly effective in liver transplant recipients. There are no data indicating that preemptive therapy for HCV infection after transplantation reduces graft loss or patient mortality, and very limited data demonstrating histologic benefit.⁴ Only approximately 1 in 5 transplant recipients experiences a sustained virologic response (SVR), less than half of that observed among nontransplant patients. The reasons for the low SVR rates are multifactorial. The percentage of transplant recipients infected with genotype 1 HCV is higher than in the nontransplant population. Since genotype 1 patients have the lowest SVR rate, most transplant recipients have a marginal chance of SVR and require a prolonged period of therapy (at least 48 weeks). Response rates are also lower due to suppression of the innate immunity, which aids in viral clearance, resulting from immunosuppressive therapy. In addition, many patients are unable to tolerate

maximal therapy. Under the current liver allocation system, a large proportion of transplantation recipients are significantly debilitated at the time of transplantation and do not physically recover until months after surgery. The constitutional side effects associated with interferon and ribavirin therapy preclude full-dose treatment in these patients in the immediate postoperative period, thereby further reducing the likelihood of achieving an SVR.

Second, most patients do not need treatment. Despite the higher rates of death and graft loss among patients with posttransplantation HCV, most patients do not develop progressive fibrosis. In addition, patients with progressive fibrosis can easily be identified with yearly protocol biopsies and treated before cirrhosis develops. Therefore, preemptive therapy introduces an unnecessary, expensive, and difficult regimen in a large group of patients who would otherwise not require treatment.

Third, treatment with interferon and ribavirin may lead to worse outcomes than would recurrent hepatitis C. The side-effect profile of pegylated interferon and ribavirin is more severe in patients receiving immunosuppressive therapy than in immunocompetent patients. The additive negative effects of immunosuppressive drugs (including calcineurin-inhibitors, azathioprine, mycophenolate mofetil, and sirolimus) and interferon on the bone marrow frequently lead to significant cytopenia in liver transplant recipients. As a result, up to 50% of patients require administration of erythropoietin and/or granulocyte-monocyte colony stimulating factor. Leukopenia caused by interferon therapy in liver transplant recipients is a particularly important clinical problem. In my experience, administration of pegylated interferon and ribavirin to liver transplant recipients is associated with a substantially higher rate of life-threatening infections, including fatal pneumonia, typhlitis, severe cellulitis, and sepsis, than is their use in patients who have not undergone transplantation. Further, the renal clearance of ribavirin is inhibited by the nephrotoxic effects of cyclosporine and tacrolimus. As a result, the administration of normal doses of ribavirin in liver transplant recipients frequently leads to increased ribavirin toxicity. Anemia is therefore a frequent complication among immunosuppressed patients. Because the biological half-life of ribavirin is prolonged in patients with reduced renal function, some patients with ribavirin-induced anemia may remain anemic for weeks or months after discontinuation of therapy. The severity of these side effects must be carefully considered prior to the initiation of treatment.

In my estimation, the best approach for managing hepatitis C following liver transplantation includes the following:

- 1) avoidance of preemptive therapy
- 2) reflexive liver biopsy for elevated liver function tests at any time after liver transplantation to rule out rejection and/or significant recurrence of HCV
- 3) protocol yearly liver biopsies to exclude progressive fibrosis in almost all patients
- 4) consideration of treatment in patients with stage 2 (of 4) or higher fibrosis.
- 5) consideration of pretransplantation treatment to eradicate HCV, thereby obviating the need for post-transplantation therapy.⁵

Trials to determine the safety and efficacy of preemptive therapy for hepatitis C in liver transplant recipients are ongoing. Until these trials are completed and further data are available demonstrating its utility, preemptive therapy seems unwarranted.

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