Outcome and Management of Hepatitis C in Liver Transplant Recipients

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Hepatitis C virus (HCV)-related cirrhosis is the leading indication for liver transplantation. Reinfection of the allograft with HCV is universal in all patients with pretransplantation viremia, and leads to histologically proven hepatitis in 50%–80% of these patients. Recent data have demonstrated significantly higher mortality among HCV-positive liver transplant recipients. For this subgroup of patients, retransplantation remains highly controversial. As current antiviral therapy is limited in efficacy and tolerability, an improved understanding of those patients at greatest risk of developing serious HCV-induced graft injury is necessary to optimize treatment.

Hepatitis C virus (HCV)-related liver disease is the leading indication for orthotopic liver transplantation (OLT) worldwide. HCV reinfection after OLT universally occurs in patients with pretransplantation viremia, and 50%–80% of these patients develop hepatitis in the graft [1]. The diagnosis is made on the basis of the presence of HCV-RNA in the serum and/or liver. Although most studies demonstrate that graft and patient survival for the first decade after OLT appears to be unaffected by the HCV serostatus of the recipient, these analyses were likely underpowered to detect small differences. Accordingly, a recent analysis of the United Network of Organ Sharing database [2] demonstrated significantly diminished survival at 5 years after primary OLT among HCV-positive patients (65.6% of HCV-negative recipients vs. 56.7% of HCV-positive recipients). Current antiviral therapy is limited in both efficacy and tolerability. Given the shortage of organs available, performance of retransplantation remains highly controversial, which highlights the importance of optimal management of recurrent hepatitis C. This review will provide a current understanding of outcome and management of the HCV-infected liver transplant recipient.

NATURAL HISTORY

The King’s College Group described the natural history of recurrent HCV infection by comparing the findings of biopsies performed according to study protocol 1 and 5 years after transplantation for OLT recipients with and without HCV infection [3]. Almost 90% of the HCV-infected patients (n = 149) had chronic hepatitis by 5 years after OLT, compared with ~20% of the HCV-negative group (n = 623; in these patients, allograft hepatitis was predominantly related to HBV infection). Of concern, the biopsy performed at year 5 revealed evidence of allograft cirrhosis in 20% of the HCV-infected patients; therefore, the natural history of HCV infection appears accelerated in OLT recipients, compared with its natural history in immunocompetent individuals. Although studies with longer follow-up are required to determine the proportion of patients who will ultimately develop allograft cirrhosis and graft failure related to recurrence of hepatitis C, it appears that <10% of patients with mild hepatitis at 1 year demonstrate progression to allograft cirrhosis at 5 years. In contrast, two-thirds of patients with at least moderate hepatitis at 1 year demonstrated progression to cirrhosis by 5 years in the King’s College series [3]. A recent study by Berenguer et al. [4] evaluated the natural history of post-OLT HCV infection by assessing the rate of progression of fibrosis. The median rate of progression of fibrosis per year was significantly higher among immunocompetent patients than it was among immunocompromised patients, and the median duration to cirrhosis was ~10 years.

What is the natural history of patients who develop allograft cirrhosis? An additional study by the Valencia group [5] eval-
uated the natural history of HCV-related graft cirrhosis to define the rate of clinical decompensation and mortality. Thirty-nine patients with clinically compensated allograft cirrhosis were studied; 18 (46%) developed at least 1 episode of decompensation, at a mean of ~8 months after transplantation. In comparison with the data generated by Fattovich et al. [6], this rate was considerably higher than it was for cirrhotic patients who did not receive transplants. Moreover, patient survival rates following development of allograft decompensation were abysmal: 93% at 1 month, 61% at 6 months, and 41% at 12 months. Variables associated with decompensation and death included a short interval between OLT and development of allograft cirrhosis and a high Child-Pugh score (score higher than A). The study concluded that if retransplantation is considered, it should be performed promptly once decompensation develops.

Clinically, recurrence of HCV infection is diagnosed on the basis of the presence of HCV-RNA in serum or in the liver allograft. Although recurrence of HCV infection is universal, there is a wide spectrum of injury detectable by biochemical and pathologic testing. The histological findings associated with recurrence can range from acute lobular hepatitis to central ballooning with cholangiolar proliferation (characteristic of the cholestatic variant). The severity of disease is based on the degree of necroinflammation and fibrosis. To date, there are no standard definitions, which may be important in determining prognosis and better identifying the subgroup of patients that would benefit from treatment.

**RISK FACTORS FOR SEVERITY OF RECURRENT DISEASE**

Several factors have been proposed to be associated with a higher rate of progression of posttransplantation fibrosis. The associated factors present before transplantation are thought to include the age of the donor [7], steatosis in the donor, and cold ischemia time [8]. After transplantation, patients who develop CMV viremia have demonstrated a greater severity of recurrent disease, likely as a result of cell-mediated immunosuppression [9]. Conversely, HCV infection is not known to induce reactivation of other viruses. Treatment against graft rejection, particularly treatment with OKT3, is known to result in perhaps the greatest risk of severe recurrent disease [10]. This highlights the importance of performing liver biopsy and prudent histological evaluation when rejection is suspected. Elevated HCV virus load, both before and after transplantation, is an established risk factor [11–13]. Whether treatment aimed at lowering the virus load is effective in reducing the risk of severe recurrent disease is not as clear.

**WHEN TO TREAT?**

Antiviral therapy for recurrent hepatitis C after liver transplantation has 4 objectives: to prevent recurrent HCV infection; to eradicate chronic HCV infection of the allograft; to prevent progressive fibrosis; and to prevent graft failure, the need for retransplantation, and death. Different strategies to achieve these goals have been proposed, based on the timing of treatment (figure 1).

Initiation of treatment could conceivably occur at any of 3 stages: before transplantation, as prophylaxis to prevent graft infection; immediately after transplantation, as preemptive therapy; or after recurrent disease is established, to prevent cirrhosis and graft failure. What remains unclear is the efficacy of these individual approaches. It is well known that current antiviral therapy is very poorly tolerated, limiting its general application. Can we justify preemptive treatment of all patients when only a subset will develop progressive allograft injury? Although it is postulated that high levels of virus in the immediate perioperative period may portend higher risk of recurrence of disease, the subset of patients that is at greatest risk of recurrent hepatitis C has yet to be identified. The following discussion will highlight the current evidence on treatment of recurrent HCV disease at its various stages.

A study by Gretch and colleagues [11] demonstrated that serum HCV RNA levels in the first 2 weeks after OLT were significantly higher among patients who subsequently developed chronic active hepatitis in their allografts than among patients who did not. A longitudinal analysis by Gane and colleagues [12] found that the onset of acute allograft hepatitis was associated with peak circulating levels of HCV RNA, which, in the majority of patients, decreased over time. Moreover, an analysis of the National Institute of Diabetes and Digestive and Kidney Diseases liver transplantation database showed the predictive value of pretransplantation virus levels: patients with circulating HCV RNA levels >1 x 10^6 eq/mL, just prior to OLT had significantly diminished graft and patient survival [13], suggesting that the size of the viral inoculum is crucial and providing a rationale for preemptive therapy in a subset of patients. On the basis of these data, some [14] have suggested that antiviral treatment should be initiated in patients with high virus loads before there is histologic evidence of recurrent disease, either prior to transplantation or within the first few weeks after transplantation. However, in a recent pilot study of 15 patients treated prior to liver transplantation, multiple, severe side effects and reduction of virus load were demonstrated in 33% of patients, and sustained viral response was not reported [15]. On the other hand, data from the University of Colorado suggest that a low, accelerating-dose antiviral regimen (IFN-α 2b, 1.5 MU t.i.w. for 2 weeks and then increased to standard 3 MU t.i.w.; ribavirin, 600 mg/day and then increased every 2 weeks to a maximum total dosage of 1200 mg/day) achieved...
sustained virologic clearance in 8 (12.5%) of 64 patients awaiting liver transplantation [16]. More importantly, 0 of the 8 patients who were HCV RNA–negative at the time of transplantation developed recurrent disease following liver transplantation. These preliminary data are highly encouraging; they suggest that viral eradication is possible in a subset of patients with end-stage liver disease, and this should translate into improved outcome after transplantation.

Similarly, treatment during the early phases of infection after liver transplantation, before graft injury has occurred, has been proposed. Mazzaferro et al. [17] report that, among 36 patients treated with combination IFN-ribavirin therapy 3 weeks after liver transplantation, 33.3% had virological eradication sustained for at least 3 years of follow-up. This suggests that early treatment, before graft damage can occur, may alter the natural history of recurrent hepatitis C after liver transplantation.

The response to IFN therapy in transplant recipients appears consistent with previous experience with immunocompetent patients who have chronic hepatitis C. However, the side effects are more poorly tolerated in the transplantation population. Several predictors for IFN nonresponse in recurrent hepatitis C include infection with HCV genotype 1, high pretreatment viremia level, inability to tolerate full-dose IFN-ribavirin therapy, and previous nonresponse to IFN. New data suggest reduced sensitivity to IFN after transplantation, as evidenced by impaired first-phase kinetics, which may further impact the therapeutic response [18].

Most of the published work has focused on treatment of established recurrent disease. IFN monotherapy has proven disappointing. Despite end-of-treatment responses, virtually all patients who had received IFN monotherapy had relapse in the immediate follow-up period. Results achieved with combination IFN-ribavirin therapy, although significantly improved compared with those achieved with monotherapy, have been overshadowed by severe side effects in a significant proportion of patients. This problem is particularly salient when one considers that most of the published trials have excluded patients with severe recurrent disease; that is, those patients for whom therapy is most likely to be cost-effective [19]. Common side effects of IFN-α include an influenza-like syndrome, depression, and dose-related myelosuppression. Up to 20% of liver transplant recipients treated with IFN require cessation of the treatment because of cytopenia [20]. The most frequent adverse side effect of ribavirin therapy is hemolysis; this is potentiated in liver transplant recipients by reduced renal clearance from calcineurin-inhibitor nephrotoxicity and HCV infection–related glomerulonephritis [20]. A recent study demonstrated the utility of measuring creatinine clearance as a predictor of need for adjustments in the dose of ribavirin for liver transplant recipients [21]. Administration of granulocyte colony-stimulating factor and erythropoietin may allow reinstitution of full-dose antiviral therapy [22].

Among patients treated with combination IFN-ribavirin, intention-to-treat end-of-treatment response rates have ranged from 27% to 53% of patients, and sustained response rates have ranged from 17% to 27% [20, 23, 24] (table 1). Unfor-
Table 1. Summary of recent literature on combination therapy to treat recurrent hepatitis C following liver transplantation.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>No. of patients</th>
<th>Duration of therapy, months</th>
<th>Treatment regimen</th>
<th>Virological response, % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>[25]</td>
<td>1997</td>
<td>21</td>
<td>6</td>
<td>IFN, 3 MU t.i.w.</td>
<td>1200</td>
</tr>
<tr>
<td>[26]</td>
<td>2001</td>
<td>40</td>
<td>12</td>
<td>IFN, 3–5 MU t.i.w.</td>
<td>1200</td>
</tr>
<tr>
<td>[22]</td>
<td>2001</td>
<td>12</td>
<td>1–17</td>
<td>IFN, 1–5 MU t.i.w.</td>
<td>600–1000</td>
</tr>
<tr>
<td>[27]</td>
<td>2001</td>
<td>18</td>
<td>12</td>
<td>IFN, 3 MU t.i.w.</td>
<td>600</td>
</tr>
<tr>
<td>[28]</td>
<td>2002</td>
<td>54</td>
<td>12</td>
<td>IFN, 3 MU t.i.w.</td>
<td>800–1000</td>
</tr>
<tr>
<td>[29]</td>
<td>2002</td>
<td>57</td>
<td>6–12</td>
<td>IFN, 3 MU t.i.w.</td>
<td>800</td>
</tr>
<tr>
<td>[30]</td>
<td>2002</td>
<td>12</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>[31]</td>
<td>2002</td>
<td>30</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NOTE. NA, not available.

* Pegylated IFN plus ribavirin was administered, but no data on dosage were given.

Unfortunately, on average, one-third of patients are unable to complete treatment because of serious drug-related adverse events [20]. The magnitude of this problem is great: 50%–90% of transplant recipients require dose reduction, compared with 10%–25% of patients who did not receive transplants. This limits the utility of antiviral therapy.

Emerging data regarding therapy with pegylated IFN and ribavirin have shown encouraging preliminary results in liver transplant recipients, with similar efficacy but improved tolerability [30–32]. A recent study of 12 patients demonstrated sustained viral response in 50% of patients after 24 weeks of combined therapy with pegylated IFN and ribavirin [30]. More data is needed to determine true efficacy and tolerability among this subgroup of patients.

**HOW LONG TO TREAT?**

Although most clinicians treat recurrent hepatitis C according to guidelines for immunocompetent patients, controlled trials are required to define the optimal duration of therapy. In this

![Figure 2. Clinical course of a patient with a recurrent case of severe cholestatic hepatitis C who cleared hepatitis C virus (HCV) RNA with standard IFN–ribavirin (RIB) treatment. After cessation of antiviral therapy, he developed relapse of cholestatic syndrome and died [33]. Month 0 corresponds to the date of transplantation. D/C, discontinuation of treatment; HCV neg, negative HCV test results; Tx, treatment; ▲, virus load; ◆, serum total bilirubin level.](https://academic.oup.com/cid/article-abstract/37/6/807/299260/18)
regard, a recent study from Italy showed a sustained virologic response rate of ~20% irrespective of whether the patients received a 6- or 12-month course of combination therapy [29]. In contrast, the subset of patients who develop severe cholestatic recurrent disease may require an indefinite duration of treatment, as suggested by our center’s own experience [33] (figure 2).

WHOM TO TREAT?

As current antiviral therapy is limited in efficacy and tolerability, treatment has traditionally been offered to patients at the greatest risk of developing allograft cirrhosis. Universally adopted criteria for initiation of treatment after transplantation include the presence of cholestatic hepatitis and severe allograft fibrosis 1 year after transplantation. In the population of patients who are awaiting liver transplantation, those with a high virus load have a greater risk of recurrent hepatitis C after transplantation. Pretransplantation prophylaxis has been theorized to eliminate the virus before transplantation. In practice, however, this strategy is limited by the safety of antiviral therapy, because many patients have relative contraindications based on hematologic indices alone.

RETRANSPLANTATION FOR RECURRENT HEPATITIS C

Whether to perform retransplantation for patients with hepatitis C is a matter of debate across the country, and the procedure is becoming less and less common at many medical centers. The magnitude of this problem is immense when one considers that ~10% of all patients who undergo liver transplantation in the United States, or ~500 patients annually, will eventually develop graft cirrhosis related to hepatitis C recurrence, which will prompt consideration of retransplantation [34]. The prospect for survival after retransplantation among unselected hepatitis C patients is not always favorable. In a study of 1539 patients undergoing liver transplantation who had identical pretransplantation characteristics, with the exception of hepatitis C status, the patients who were HCV-positive had a 1.36-fold greater mortality risk than did the patients who were not [35]. More recently, a study by Berenguer et al. [36] of 12 HCV-positive patients who underwent retransplantation demonstrated that recurrence of hepatitis C is very aggressive, mirroring that seen after the first transplantation, and is associated with significant mortality.

FUTURE CONSIDERATIONS

The evolution of our understanding of the natural history and management of HCV infection in the liver transplant recipient has been rapid in the past decade. However, factors for identifying patients at increased risk for progression of underlying liver disease and for predicting the severity of recurrent disease in liver transplant recipients are incompletely understood. Hopefully, effective and safe prophylactic and therapeutic regimens will be developed that alter the natural history of HCV infection and diminish the rate of patient death and graft loss. Nonhemolyzing ribavirin substitutes are under investigation, including levovirin, an analogue and l-enantiomer of ribavirin, which has immunomodulatory effects in the mouse model that are similar to those of ribavirin and has an improved safety profile [37]. In addition, as knowledge regarding the effects of immunosuppression expands, we may be able to administer regimens that favorably alter the natural history of recurrent hepatitis C disease.

References

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