

# Management of Recurrent Hepatitis C Following Liver Transplantation

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**Abstract:** Hepatitis C virus (HCV) is the most common indication for liver transplantation in the United States, and recurrent disease associated with HCV is a major cause of allograft loss and mortality. Up to 30% of transplant recipients with HCV will develop progressive fibrosis and cirrhosis within 5 years of transplantation. Several recipient, donor, and viral factors have been identified as risk factors for disease progression. Likewise, immunosuppression with pulse corticosteroids or T-cell-depleting therapies such as muromonab-CD3 have been linked to HCV-associated allograft failure. Antiviral therapy with peginterferon alfa and ribavirin should be considered in select transplant recipients with recurrent HCV infection, as achievement of sustained virologic response is associated with increased allograft and patient survival; however, efficacy may be limited by poor tolerability, requirement for dose reductions, and treatment discontinuation. The use of emerging therapies such as direct-acting antiviral agents and steroid-sparing immunosuppression may play a major role in further advances associated with post-transplant management of recurrent HCV infection.

Hepatitis C virus (HCV) is the most common chronic blood-borne infection in the United States, affecting over 4 million individuals, with a prevalence of approximately 1.6%.<sup>1</sup> Recent reports have suggested that up to two thirds of newly diagnosed chronic liver disease in the United States results from HCV.<sup>2</sup> Most individuals exposed to HCV during adulthood develop chronic infection, and up to 20% may progress to end-stage liver disease.<sup>3</sup> Consequently, chronic HCV infection has become a major source of liver-related mortality. The prevalence of HCV-associated advanced liver disease is expected to rise over the next several decades.<sup>4</sup> HCV is currently the most frequent indication for liver transplantation, comprising approximately 40–50% of all cases.<sup>5,6</sup>

As recurrence of HCV occurs in all liver transplant recipients who demonstrate hepatitis C viremia at the time of transplantation, the potential for progressive disease in the transplanted liver is a major concern. Although an improvement in patient and allograft

## Keywords

Hepatitis C virus, liver transplant, recurrence, immunosuppression, interferon, ribavirin

survival has been described recently,<sup>7,8</sup> in contrast to previous reports,<sup>9</sup> the presence of HCV infection remains an independent risk factor for increased mortality following liver transplantation.<sup>10,11</sup> Recipient, donor, and viral factors, as well as immunosuppressive therapies, may contribute significantly to the severity of liver disease associated with recurrent HCV. In order to achieve the goal of optimal patient and allograft survival in patients with HCV undergoing liver transplantation, several strategies have emerged, including donor selection, close histologic monitoring, interferon (IFN)-based therapy, and steroid-sparing immunosuppression.

## Hepatitis C and the Transplanted Liver

### *Recurrence of Chronic Infection*

Recurrence of hepatitis C viremia following liver transplantation occurs in all patients with chronic HCV infection who have detectable serum HCV RNA levels prior to transplant. A significant decline in serum HCV RNA levels has been observed during the anhepatic phase of transplantation and immediately following reperfusion of the allograft; however, this decline is followed by a rapid increase in HCV RNA levels within hours, and pretransplantation serum HCV RNA levels can be reached within days.<sup>12,13</sup> A progressive rise in HCV RNA levels has been described over several weeks following transplantation, resulting in a new baseline viral load that is typically greater than the viral load prior to transplant.

Acute hepatitis associated with recurrent HCV infection can be seen in over one half of patients, typically within the first 6 months of transplant.<sup>14</sup> This finding may be associated with an acute rise in serum aminotransferase levels, increased viral load, and histologic evidence of acute hepatitis C infection with features such as lobular hepatitis, the presence of acidophil bodies, macrovesicular steatosis, and focal hepatocellular necrosis.<sup>14,15</sup> Up to 30% of patients may subsequently develop chronic hepatitis with a variable clinical course, characterized by progressive fibrosis leading to cirrhosis within 5 years.<sup>16</sup> The development of cirrhosis in the setting of recurrent HCV infection following transplant is associated with an accelerated course and has a significant impact on survival. Clinical decompensation may occur in over 40% of patients with allograft cirrhosis within 1 year, at which time 1-year survival may decrease to as low as 40%.<sup>17</sup>

### *Fibrosing Cholestatic Hepatitis C*

Although it occurs in less than 10% of transplant recipients with chronic HCV, a severe and rapidly progressive form of recurrent HCV infection characterized by cholestatic disease has a major impact on survival. In contrast to a chronic hepatitis observed in most patients

with recurrent HCV, this syndrome is defined by a total serum bilirubin of more than 6 mg/dL, elevated alkaline phosphatase or gamma glutamyltransferase levels more than 5 times the upper limit of normal, high serum HCV RNA levels, and histologic features including central hepatocyte ballooning without necrosis, cholangiolar proliferation without loss of bile ducts, and intrahepatic cholestasis in the absence of significant inflammation, biliary obstructive disease, or vascular complications.<sup>15,18</sup> Onset typically occurs within the first 6 months following liver transplantation, and rapid progression to allograft failure may occur within 1 year.<sup>19</sup> In addition, patient survival following repeat liver transplantation for fibrosing cholestatic HCV is severely compromised; thus, retransplantation is not an acceptable management option in this case.<sup>15</sup>

### *Risk Factors for Severe Liver Disease*

Several recipient, donor, and viral factors, as well as the use of specific immunosuppressive agents, have been identified as risk factors for increased severity of disease progression, allograft loss, and decreased survival in patients with HCV who undergo liver transplantation (Table 1).<sup>15,18</sup> The presence of a severe histologic grade of inflammation early in the post-transplant course, particularly within the first year, may be predictive of more rapid fibrosis progression and cirrhosis at 5 years.<sup>18,20</sup> Elevated serum HCV RNA levels both prior to undergoing transplant and during the post-transplant period may also be associated with progressive disease.<sup>20,21</sup> Donor age has been identified as a major risk factor, as increased age, particularly over 50 years, is associated with more rapid disease progression, development of cirrhosis, and HCV-associated graft failure.<sup>15,16,22</sup> Additional factors that may potentially be associated with severe recurrent disease include infection

**Table 1.** Established Risk Factors for Severe Recurrent Hepatitis C Virus (HCV) Following Liver Transplantation

- Fibrosing cholestatic HCV syndrome
- Increased serum HCV RNA levels (pre- or post-transplantation)
- Early recurrence or severe histologic inflammatory activity within 1 year
- Use of high-dose intravenous pulse corticosteroids or muromonab-CD3
- Increased donor age
- Cytomegalovirus infection
- HIV-HCV co-infection

Reproduced from Wiesner RH, et al.<sup>15</sup> and Gane EJ.<sup>18</sup>

with HCV genotype 1, presence of cryoglobulinemia, female gender, increased recipient age, non-white ethnicity of recipient, donor steatosis, and cold ischemia time. However, data that strongly support these factors, specifically in association with HCV disease progression, are limited or, in some cases, conflicting.<sup>15</sup>

Cytomegalovirus (CMV) infection is common in liver transplant recipients and is a major risk factor for severe recurrence of HCV-associated liver disease. HCV patients who develop CMV viremia following liver transplantation are at an increased risk of advanced histologic changes, including periportal and bridging necrosis, lobular inflammatory activity, and development of cirrhosis.<sup>23</sup> The greatest risk of CMV disease occurs in the setting of donor CMV seropositivity and recipient seronegativity. Prophylaxis or preemptive therapy have been described as a means of preventing CMV infection in at-risk individuals. Prophylaxis with valganciclovir for 3 months following liver transplantation has been reported as the most common strategy utilized in this population.<sup>24</sup>

Immunosuppression may have a significant impact on the risk of disease progression following transplant. Viral kinetics studies have described a rapid increase in serum HCV RNA levels in patients who receive high-dose intravenous corticosteroids intraoperatively<sup>13</sup> or in the treatment of acute cellular rejection.<sup>12</sup> Further studies have identified the use of pulse intravenous corticosteroid therapy or muromonab-CD3 (Orthoclone OKT3, Ortho Biotech; an anti-CD3 monoclonal antibody) as independent risk factors for development of cirrhosis and graft failure.<sup>16,25</sup> Results of prospective studies evaluating outcomes in HIV-HCV co-infected individuals have revealed significantly reduced post-transplant survival in co-infected patients compared to other HIV-positive or non-HIV transplant recipients, with 3- and 5-year survival rates as low as 56% and 33%, respectively.<sup>26,27</sup> In particular, HIV-HCV co-infected patients with CD4+ cell counts less than 200 cells/ $\mu$ L are at an increased risk, indicating the negative impact of an immunocompromised state in the setting of immunosuppressive therapy following transplantation. Additional factors associated with decreased survival in this population include elevated post-transplant HIV or HCV viral load, intolerance to antiretroviral therapy, and African American ethnicity.<sup>26,27</sup>

### **Post-Transplant Monitoring**

The most accurate means of testing for the presence of HCV-associated disease resulting from recurrent HCV infection is a liver biopsy. Although elevations in serum aminotransferase and HCV RNA levels may occur in the setting of HCV recurrence, histopathologic assessment by an experienced pathologist provides the most definitive

diagnostic information and is critical to distinguishing between recurrent HCV and other disease processes, including acute or chronic rejection, biliary disease, or other viral infections such as CMV. Annual liver biopsies are recommended in HCV liver transplant recipients in order to assess for progressive allograft fibrosis and potential candidacy for antiviral therapy, as combination peginterferon alfa (PegIFN) and ribavirin (RBV) should be considered in patients with histologic evidence of recurrent HCV and stage 2 fibrosis.<sup>15</sup>

## **Antiviral Therapy**

### **Treatment Before Transplantation**

Although PegIFN in combination with RBV remains the gold standard for the treatment of chronic HCV infection in the pretransplant setting,<sup>28,29</sup> long-term viral suppression can be achieved in only approximately one half of patients.<sup>30,31</sup> Antiviral therapy in patients with HCV cirrhosis awaiting liver transplantation should be considered in select individuals; however, poor tolerability may limit virologic response. Although successful response to PegIFN therapy has been described in compensated cirrhotics,<sup>32,33</sup> sustained virologic response (SVR) can be significantly reduced in those with decompensated disease.<sup>34,35</sup> Up to 50% of decompensated cirrhotics may experience significant hematologic side effects associated with PegIFN and RBV, leading to dose reductions and treatment discontinuation. Consequently, low SVR rates have been reported in 7–13% of genotype 1 patients and up to 50% of nongenotype 1 patients.<sup>34,35</sup> In light of the potential benefit of viral eradication and avoidance of allograft re-infection, antiviral therapy prior to liver transplantation is recommended in patients who are candidates, primarily those with Child-Turcotte-Pugh scores of no more than 7 and model for end-stage liver disease (MELD) scores of no more than 18.<sup>15</sup>

### **Post-Transplant Strategies**

The principal strategies that have emerged involving antiviral therapy for recurrent HCV include a preemptive approach (with initiation of treatment immediately following transplantation) and a recurrence-based approach (in which treatment candidates are selected based upon histologic evidence of HCV-associated liver disease). An advantage of the preemptive strategy is the ability to initiate therapy when serum HCV RNA levels are characteristically low; however, selecting candidates able to tolerate therapy at an early time point following transplantation is a major challenge. Prospective studies evaluating a preemptive approach with IFN-based therapy are limited.<sup>36–41</sup> Only 2 small trials have evaluated the efficacy of PegIFN in this setting (Table 2),<sup>40,41</sup> one of which noted

**Table 2.** Prospective Clinical Trials of Preemptive Peginterferon Alfa for Recurrent Hepatitis C Following Liver Transplantation

| Study                              | Treatment arms*         | Patients (n) | Genotype 1 (%) | SVR (%) | Discontinuation (%) | Dose reduction (%) |
|------------------------------------|-------------------------|--------------|----------------|---------|---------------------|--------------------|
| Shergill AK, et al. <sup>40†</sup> | IFN-2b or PegIFN-2b     | 22           | —              | 5       | 37                  | 85                 |
|                                    | IFN-2b or PegIFN-2b/RBV | 22           |                | 18      |                     |                    |
| Chalasani N, et al. <sup>41</sup>  | PegIFN-2a               | 26           | 73             | 8       | 31                  | 42                 |
|                                    | No treatment            | 28           | 75             | 0       |                     |                    |

\*Both studies reported a treatment duration of 48 weeks. (—) designates data not provided or not applicable.

†Patients received IFN-2b (n=34) or PegIFN-2b (n=10) based upon the standard of care at the time of enrollment in the trial.

IFN=interferon alfa; PegIFN=peginterferon alfa; RBV=ribavirin; SVR=sustained virologic response.

that only 41% of screened transplant recipients were eligible to begin therapy.<sup>40</sup> These studies reported a relatively low SVR (5–18%) following 48 weeks of PegIFN-based therapy, as well as discontinuation in approximately one third of patients and dose reductions in up to 85%.<sup>40,41</sup>

Recurrence-based strategies of antiviral therapy in HCV transplant recipients have been more extensively studied,<sup>42</sup> though prospective comparative clinical trials with treatment arms including PegIFN are limited. Based upon these studies, the SVR associated with PegIFN therapy in predominantly genotype 1–infected populations has been reported to range from 12% to as high as 50% (Table 3).<sup>41,43–48</sup> A recent extensive review of prospective and retrospective clinical studies describing antiviral therapy with combination PegIFN and RBV in this population reported a mean SVR of 30%.<sup>42</sup> It is important to note that not only have these studies reported a wide range of success rates, but they also vary greatly in factors such as the choice of immunosuppressive regimens, inclusion criteria, and timing of antiviral therapy. As noted in the preemptive approach, treatment of established HCV recurrence may be significantly limited by patient tolerability, with treatment being discontinued in up to one third of patients and dose reductions required in the majority of patients.<sup>41–45,47,48</sup> In patients with advanced fibrosis or cholestatic hepatitis, discontinuation of therapy may occur in over 50%.<sup>45</sup> Extended duration antiviral therapy has also been described in patients with established recurrent HCV; however, no clear long-term benefit of this treatment approach has been established.<sup>49,50</sup>

It is evident that more controlled prospective data are required in order to determine the safest and most effective treatment approach in this population, with the goals of achieving HCV eradication and prevention of progressive liver disease. The results of 2 multicenter prospective studies assessing the safety, efficacy, and benefit of preemptive or recurrence-based antiviral therapy, respectively, have recently been presented in abstract form.<sup>51,52</sup>

The PHOENIX (Pegasys and Copegus Administered After Liver Transplantation for Hepatitis C) trial randomized patients after liver transplantation to receive 48 weeks of preemptive combination therapy or to undergo observation with the potential for treatment initiation once histologic evidence of recurrent HCV was established. A relatively low SVR was found in 22% of patients who received preemptive therapy, as well as discontinuation of therapy in over 40%, and increased reports of hematologic side effects.<sup>51</sup> The PROTECT (Pegylated Interferon Alfa-2b and Ribavirin After Orthotopic Liver Transplantation: Efficacy and Safety in Hepatitis C Recurrence Therapy) study evaluated the treatment of established recurrent HCV following liver transplantation. Although the overall reported SVR was 29%, sustained response rates were over 50% in genotype 2 or 3 patients and in those who were able to complete a course of therapy. Similar to previous reports, hematologic side effects were prevalent; over 50% of patients required dose reductions; and up to 30% of patients discontinued therapy.<sup>52</sup>

#### *Predictors of Sustained Viral Clearance*

Achievement of SVR in the setting of recurrent HCV following liver transplantation may have a major impact on long-term outcomes, including improved graft and patient survival.<sup>53–55</sup> Identifying patients with a greater likelihood of achieving SVR is an important consideration in the selection of potential treatment candidates and is a key factor in developing strategies for optimizing response to therapy. HCV genotype remains an important predictor of SVR in the post-transplant setting, as sustained clearance may be significantly higher in non-genotype 1 patients, with reported SVR rates greater than 60%, particularly in patients with HCV genotype 2 or 3 infection.<sup>42</sup> The most important predictor of successful response during a course of antiviral therapy before transplant is the serum HCV RNA level, with achievement of rapid virologic response (RVR) at week 4 and

**Table 3.** Comparative Prospective Clinical Trials of Peginterferon Alfa in the Treatment of Established Recurrent Hepatitis C Virus Following Liver Transplantation

| Study                               | Treatment arms*           | Patients (n) | Genotype 1 (%)  | SVR (%) | PegIFN DC (%) | PegIFN DR (%)   | RBV DR (%)      |
|-------------------------------------|---------------------------|--------------|-----------------|---------|---------------|-----------------|-----------------|
| Chalasanani N, et al. <sup>41</sup> | PegIFN-2a                 | 34           | 79              | 12      | 30            | 61              | —               |
|                                     | No treatment              | 33           | 75              | 0       |               |                 |                 |
| Castells L, et al. <sup>43</sup>    | PegIFN-2b/RBV             | 24           | 100             | 35      | 0             | 25              | 58              |
|                                     | No treatment              | 24           |                 | 0       |               |                 |                 |
| Angelico M, et al. <sup>44</sup>    | PegIFN-2a/RBV             | 21           | 81              | 33      | 33            | 38              | 75 <sup>†</sup> |
|                                     | PegIFN-2a                 | 21           | 86              | 38      | 28            | 33              |                 |
| Carrion JA, et al. <sup>45‡</sup>   | PegIFN-2b/RBV (F0-F2)     | 27           | 85              | 48      | 22            | 11              | 67              |
|                                     | PegIFN-2b/RBV (F3-F4, CH) | 27           | 100             | 19      | 56            | 37              | 67              |
|                                     | No treatment (F0-F2)      | 27           | 85              | 0       |               |                 |                 |
| Bizollon T, et al. <sup>46</sup>    | PegIFN-2b/RBV             | 27           | 74              | 30      | 7             | —               | —               |
|                                     | No treatment              | 21           | 86              | 0       |               |                 |                 |
| Nair S, et al. <sup>47</sup>        | PegIFN-2b/RBV             | 45           | 80 <sup>§</sup> | 50      | —             | 62 <sup>‡</sup> | 66              |
|                                     | PegIFN-2b/RBV/amantadine  |              |                 | 26      |               |                 |                 |
| Firpi RJ, et al. <sup>48</sup>      | PegIFN-2a/RBV/TAC         | 20           | 85              | 35      | 10            | 60              | 90              |
|                                     | PegIFN-2a/RBV/CSA         | 18           | 94              | 39      | 17            | 94              | 89              |

\*All studies reported a treatment duration of 48 weeks except Bizollon T, et al.,<sup>46</sup> in which nongenotype 1 patients received 24 weeks of treatment. (—) designates data not provided or not applicable.

<sup>†</sup>A low-accelerating dose regimen of RBV was used. Dose-reduction data are provided for patients receiving 800 mg RBV daily. No patients tolerated more than 800 mg RBV daily.

<sup>‡</sup>Patients with mild (F0-F1) fibrosis stage were randomized to receive PegIFN/RBV or no treatment. A treatment arm with advanced (F2-F3) fibrosis stage or cholestatic hepatitis also received PegIFN/RBV.

<sup>§</sup>Genotype data are based upon per-protocol analysis.

<sup>††</sup>Value includes PegIFN discontinuations.

CH=cholestatic hepatitis; CSA=cyclosporine; DC=discontinuation; DR=dose reduction; PegIFN=peginterferon alfa; RBV=ribavirin; SVR=sustained virologic response; TAC=tacrolimus.

early virologic response (EVR) at week 12 providing the highest positive and negative predictive values of SVR, respectively.<sup>31,56,57</sup> In the post-transplant setting, rapid HCV clearance during therapy is also a key predictor of sustained response, as demonstrated in several prospective studies,<sup>43,44,46,47</sup> including the PROTECT study, in which the greatest response was observed in those who cleared HCV within 4 weeks (RVR), followed by those who achieved viral clearance within 12 weeks (complete EVR).<sup>52</sup>

### Tolerance and Safety

A major limitation of both preemptive therapy and treatment of established HCV recurrence is tolerability, particularly with respect to the hematologic side effects of PegIFN and RBV. An additional factor that must also be addressed in this population is renal dysfunction and the

potential for RBV toxicity. As with patients undergoing antiviral therapy in the nontransplant setting,<sup>58,59</sup> adherence to both PegIFN and RBV based upon the administered dose and duration of therapy appears to have a major impact on the ability to achieve viral clearance in patients who have undergone liver transplantation. Thus, poor tolerance may contribute significantly to the lower overall SVR observed in the setting of recurrent HCV. The use of growth factors to minimize the potential for hematologic side effects associated with PegIFN and RBV (such as anemia and neutropenia) may have a particularly important role in this population. Although IFN-based therapy has been associated with an increased risk of kidney allograft rejection in kidney transplant recipients,<sup>60</sup> prospective studies in liver transplant recipients have not reported an increased risk of liver allograft rejection.<sup>41,43-46,51,52</sup> The ability to optimize adherence to both therapy and viral

clearance will continue to be an important consideration in the development of strategies utilizing IFN-based regimens in patients with recurrent HCV.

## Immunosuppression

Immunosuppressive regimens initiated at the time of liver transplantation, as well as methods of treating acute cellular rejection during the post-transplant course, appear to have a significant role in the development of liver disease associated with HCV recurrence.<sup>12,13,16,25</sup> Consequently, several strategies have emerged with the goal of minimizing the negative impact of high-dose or pulse corticosteroids. Some data have suggested that a treatment approach characterized by slow tapering of corticosteroids following transplantation may be associated with a reduced severity of recurrent HCV and fibrosis progression, in contrast to more rapid or abrupt decreases in corticosteroid doses.<sup>22,61-63</sup> It is not clear that avoiding corticosteroids entirely may result in improved long-term outcomes; however, a recent meta-analysis noted a potential decrease in the risk of recurrent HCV based upon histologic parameters in addition to a decrease in the risk of CMV infection.<sup>64</sup>

The use of highly specific monoclonal antibody therapy has recently been introduced as an alternative approach to corticosteroids in liver transplant recipients with HCV. The interleukin (IL)-2 receptor antagonists, daclizumab (Zenapax, Hoffman-La Roche; humanized) and basiliximab (Simulect, Novartis; chimeric), are monoclonal antibodies that avidly bind to the alpha subunit (CD25) of the IL-2 receptor, leading to inhibition of activated T lymphocytes. Both daclizumab and basiliximab have been used successfully in patients with HCV as induction immunosuppressive agents in steroid-free regimens.<sup>65-69</sup> In these clinical trials, the incidence of allograft rejection in steroid-free arms was decreased<sup>65-67</sup> or not significantly different<sup>68,69</sup> compared to regimens that included steroids. Although these agents are viable alternatives in transplant recipients with HCV, studies thus far have not demonstrated any significant benefit with regard to HCV recurrence, fibrosis progression, or survival after 1–2 years of follow-up.<sup>65,66,68</sup>

Cyclosporine (CSA) is a widely used immunosuppressive agent that may have a direct inhibitory effect on HCV replication. CSA, as well as CSA analogues without immunosuppressive properties such as NIM811 and DEBIO-25, have demonstrated *in vitro* activity against HCV via inhibition of cyclophilins, which are cellular proteins involved in HCV nonstructural protein binding and viral replication within the host.<sup>70-73</sup> Retrospective data have suggested increased SVR rates in patients undergoing antiviral therapy with PegIFN and RBV who receive CSA-based immunosuppression.<sup>71,74</sup>

Although lower serum HCV RNA levels were described in patients undergoing antiviral therapy who converted to a CSA-based regimen, a recent prospective, randomized, pilot study did not reveal a significant difference in SVR compared to those who received tacrolimus (TAC).<sup>48</sup> Additional data have not demonstrated a significant difference in long-term outcomes between CSA and TAC, including endpoints such as patient or graft survival and incidence of rejection.<sup>75</sup> Whether the use of CSA in liver transplant recipients with HCV will have long-term benefit or whether conversion of immunosuppression to a CSA-based regimen during antiviral therapy is warranted will require further prospective investigation.

## Repeat Liver Transplantation

Ultimately, repeat liver transplantation may be considered in select patients with HCV recurrence and allograft failure. Although prior data have identified HCV infection as an independent predictor of mortality following retransplantation,<sup>76</sup> more recent reports have described similar rates of survival in HCV and non-HCV recipients.<sup>77-79</sup> A key factor associated with the observed improvement in outcomes related to retransplantation for recurrent HCV is patient selection. It is well recognized that the development of fibrosing cholestatic HCV is a major risk factor for severe recurrent disease following repeat transplantation with a negative impact on post-transplant survival.<sup>15</sup> In a recent multicenter retrospective study that reported similar survival in HCV-infected and non-HCV patients listed for retransplantation, the most common reasons for not relisting potential candidates included rapid recurrence of HCV within 6 months and fibrosing cholestatic HCV.<sup>79</sup> A recent review of the United Network for Organ Sharing database noted improved 1-year patient and graft survival in HCV-infected individuals undergoing repeat transplantation over subsequent study periods from 1994 to 2005.<sup>80</sup> In this study, factors independently associated with an increased risk of mortality following retransplantation in patients with HCV included increased recipient age, MELD score greater than 25, retransplantation within 1 year of the first transplant, donor age 60 years or greater, and prolonged warm ischemia time. These findings emphasize the importance of not only patient selection, but also donor selection when considering repeat liver transplantation in patients with recurrent HCV.

## Long-Term Strategies and Future Therapies

The development of post-liver transplantation comorbidities, including obesity, hypertension, hyperlipidemia, diabetes mellitus, and renal insufficiency are of particular importance in patients with chronic HCV because they may greatly influence the course of recurrent disease.

Post-transplant metabolic syndrome is common and may occur in up to one half of patients.<sup>81</sup> Although components of metabolic syndrome are largely associated with immunosuppressive agents such as corticosteroids and calcineurin inhibitors, emerging data have revealed that HCV infection itself is a risk factor for its development. Recent studies have noted an increased incidence of insulin resistance and new onset diabetes mellitus within the first year in transplant recipients with HCV in contrast to non-HCV recipients.<sup>82,83</sup> Consequently, the effects of insulin resistance in transplant recipients with HCV can be significant, as the development of insulin resistance has been linked to an increased risk of progressive liver disease and advanced allograft fibrosis.<sup>84</sup> Efforts to minimize the development of post-transplant metabolic syndrome through steroid-free immunosuppression, minimization of calcineurin inhibitor therapy, and aggressive treatment of metabolic complications as they arise may become increasingly important in achieving optimal long-term clinical outcomes in HCV liver transplant recipients.

New investigational antiviral agents with selective activity against various phases of the HCV life cycle and replication, known as direct-acting antiviral (DAA) agents, will likely contribute greatly to the development of more effective treatment strategies against chronic HCV infection. These new agents include protease inhibitors, polymerase inhibitors, immune modulators, cyclophilin inhibitors, ribavirin analogues, and other molecules. Antiviral regimens involving the protease inhibitors telaprevir and boceprevir, in particular, have demonstrated significant improvements over combination PegIFN and RBV in phase II randomized clinical trials.<sup>85-87</sup> Although DAA agents have not been studied in the transplant setting, they will likely have an important role in the treatment of HCV before or after transplantation, as they may potentially enhance the ability to achieve SVR with a shorter course of therapy. Additional treatment strategies involving CSA-based or steroid-sparing immunosuppression will require further prospective investigation. Other clinical tools, including the detection of specific genetic polymorphisms that are predictive of response to antiviral therapy (such as the IL-28B polymorphism),<sup>88</sup> may also guide individualized treatment strategies in this population.

## Summary

Recurrent HCV is a major cause of allograft loss and mortality in liver transplant recipients with chronic HCV infection. The development of strategies designed to optimize patient and graft survival in this population is critical, as HCV is currently the most common indication for liver transplantation. A greater understanding of

the risk factors for progressive disease and vigilant post-transplant monitoring through histologic assessment may guide management aimed toward reducing the potential for graft failure as well as helping identify candidates for antiviral therapy. As treatment with PegIFN and RBV may not be possible in many patients awaiting liver transplantation, post-transplant antiviral therapy is a consideration in select individuals; however, major limitations of both preemptive and recurrence-based therapy include poor tolerability and decreased efficacy. The emergence of DAA agents targeted specifically against HCV may ultimately have a major impact on the ability to achieve viral eradication both before and after transplantation. Likewise, increasing recognition and avoidance of post-transplant metabolic complications as well as the development of novel immunosuppression strategies, including the use of steroid-sparing agents, may potentially improve long-term outcomes in transplant recipients with chronic HCV.

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