Management of Hepatitis C Virus Infection in the Setting of Liver Transplantation

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Key Points
1. Posttransplantation recurrence of hepatitis C virus infection is a universal phenomenon with a highly variable natural history.
2. Approximately 10% to 25% of hepatitis C virus–infected recipients of liver allografts will develop cirrhosis within 5 years after transplantation.
3. The 1-year actuarial risk of hepatic decompensation after recurrence of cirrhosis approximates 42%.
4. Some of the factors associated with aggressive recurrence include donor and recipient age, recent year of transplantation, recipient gender and race, the use of antithymocyte globulin, and high dose of corticosteroids.
5. Highly aggressive recurrent hepatitis C virus infection leading to cirrhosis fares poorly after retransplantation in the presence of hyperbilirubinemia and renal failure, with a 1-year survival of approximately 40%.
6. Elevated serum aminotransferases are a poor indicator or recurrent disease.
7. Current sustained virological response after combination pegylated alpha interferon and ribavirin treatment is approximately 25%.
8. There is no consensus on initiation time point, duration of treatment, or dosage. Given immunosuppression, at least 48 weeks of therapy is a reasonable approach.
9. Treatment for 48 weeks is cost effective. Incremental cost-effectiveness ratio for men aged 55 years is $29,100 per life-year saved.

Chronic hepatitis C virus (HCV) infection is common and affects a significant proportion of the world population, with an estimated 170 million people infected and 3 to 4 million new cases per year.1,2 HCV-related cirrhosis is the most common indication for liver transplantation (LT) in the United States and most European countries.3-7 In the United States, over one-third of available liver allografts are transplanted into recipients with chronic HCV infection. In fact, despite a decline in the incidence of new HCV cases, the prevalence of infection will not peak until the year 2040.5 As the duration of infection increases, the number of new patients with cirrhosis will double by the year 2020 in an untreated patient population.5 If this model is correct, the projected increase in the need for LT secondary to chronic HCV infection will place a burden that may be impossible to meet on an already limited supply of organ donors.

In this article, we review the natural history of HCV in the transplantation population, risk factors associated with severity of recurrence, histological changes associated with recurrence of disease, treatment strategies, and the role of retransplantation.

Natural History of Recurrent HCV Infection

Virological Recurrence

The clinical history of recurrent HCV infection as defined by detectable HCV RNA in serum is almost a universal phenomenon.4,8-12 Reinfection of the liver allograft has been recognized at the virological level by either an increasing level of serum HCV RNA or detection of HCV RNA in the allograft itself.13 In fact, while the interval between LT and clinical allograft infection varies, the presence of negative-strand HCV RNA, the sine qua non of HCV replication, in serum has been recorded as early as 48 hours after LT and hepatocyte expression of HCV antigens as early as 10 days after LT (25% of patients).11,12,14,15 A recent study of post-LT hepatitis C viral kinetics showed that the first round of infection likely occurs during reperfusion of the graft. In this study, serum viral levels reached pre-LT titers by postoperative day 4 in a significant number of patients. Viral load then tended to increase over the ensuing weeks, reaching a plateau at approximately 1 month after LT.16 Serum levels of HCV RNA peak at 1 to 3 months, achieving 1-year post-LT levels that are 10- to 100-fold greater than the mean pre-LT levels.13,17 Viral titers at 1 year after LT usually plateau at 1 to 2 logs higher than pre-LT levels.

Abbreviations: HCV, hepatitis C virus; LT, liver transplantation; ACR, acute cellular rejection; FCH, fibrosing cholestatic hepatitis.

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Progression of Disease

The course of post-LT HCV is highly variable. However, the histological progression of chronic hepatitis C is more aggressive and is associated with a reduction in patient and graft survival when compared to non-HCV transplant recipients.8,22-29 Several small single-center studies and one large retrospective analysis of the United Network for Organ Sharing transplant registry have shown a decreased survival for patients who undergo transplantation for HCV infection. In the latter study, Forman and coworkers identified an increased rate of death (hazard ratio, 1.23) and graft loss (hazard ratio, 1.30) at 1, 3, and 5 years after LT for HCV-positive recipients vs. HCV-negative recipients.22

The median rate of fibrosis progression in the post-LT population (based on the Desmet fibrosis score of 0 to 4) is estimated to be between 0.3 and 0.8 stages per year in HCV-infected liver recipients vs. 0.1 to 0.2 stages per year in immunocompetent HCV-infected patients. The median interval from transplantation to cirrhosis is 10 years compared with 20 to 40 years in immunocompetent patients.23,30,31

Recurrent HCV infection is a highly dynamic process. It has been estimated that the balance between hepatocellular apoptosis and regeneration might be active enough to lead to replacement of the entire transplanted liver in 2 weeks.14 Recurrent infection is characterized by progression to cirrhosis in 6 to 23% of the patients at a median of 3 to 4 years after LT, with a cumulative probability of developing graft cirrhosis of 30% at 5 years (vs. 5% in the nontransplant population) (Fig. 1).8,24,28,30,32-34 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.35 Once cirrhosis develops, the rate of progression from hepatic decompensation to death is strikingly accelerated compared with immunocompetent non-transplant HCV-infected patients.33,36,37 Approximately 10% to 25% of HCV infected recipients of liver allografts with recurrent disease will die or require retransplantation within 5 years after transplantation.38

The role of the immune system in the pathogenesis of recurrent chronic HCV infection is only partially understood. In immunocompetent individuals, a key element in the development of chronic infection is HCV-mediated interference with a robust T-helper subtype 1 (T_{H1}) CD4 response and recruitment with activation of cytotoxic T cells. This inability to generate an effective immune response is at least one factor that favors the establishment of infection and maintenance of chronicity.39 An immunosuppressed state would hypothetically further compromise this response. Supporting further this hypothesis, a study by Rosen and coworkers found that despite immunosuppression, some LT recipients show HCV-specific major histocompatibility complex class II–restricted CD4^+ T-cell responses and experience minimal or no histological recurrence after liver transplantation vs. severe recurrence in LT recipients who lack appropriate immunologic responses to HCV antigens.40 These findings suggest that the inability to generate a virus-specific T-cell response plays a contributory role in the pathogenesis of HCV-related graft injury after liver transplantation.40

Biochemical and Histological Patterns of HCV Recurrence

Early reinfection of the liver allograft and the subsequent increase in HCV level correlate poorly with an increase in serum aminotransferases. Elevated serum aminotransferases lack sensitivity and specificity (rejection, ischemia, opportunistic infections, etc.) in the post-LT population. Approximately 20% to 30% of patients with chronic HCV disease have persistently normal serum alanine aminotransferase levels and never develop biochemical or clinical hepatitis after LT.8,41 In addition, histological differences between HCV-infected and non–HCV-infected allografts in the early post-LT period are difficult to detect, as histological injury at this stage is usually dominated by allograft rejection or preservation-reperfusion injury.12 More obvious hepatitis is evident at 1 to 3 months after LT, when all patients are serum HCV RNA positive, and HCV core antigen can be detected in more than 90% of biopsy specimens.11,12,14,42 It is this clinical and histological recurrence of hepatic disease that is critical to
define so that future observations can lead to a consensus on diagnosis and treatment. The nonspecific biochemical presentation of recurrent HCV infection highlights the usefulness of protocol biopsies in this population.

The diagnosis of acute HCV infection in the allograft should be based on the presence of typical histologic features that parallel those in the non-LT population. The time to appearance is not a strict defining criterion of acute vs. chronic disease in this setting, as acute HCV disease may arise at variable points in the post-LT course. Thus, histological confirmation of HCV disease is essential for the diagnosis of recurrent HCV infection with the exclusion of acute cellular rejection (ACR). Unfortunately, the interobserver and intraobserver agreement rate for the differentiation of ACR vs. recurrent HCV infection has low reliability.

Differentiation of ACR from recurrent HCV infection represents one of the most difficult challenges in the care of post-LT patients infected with HCV. At the histological level, the diagnosis of ACR in the setting of recurrent HCV disease is likely to depend on the presence of endothelitis, severe bile duct damage, and characteristics of the portal tract infiltrate (mononuclear infiltrate in chronic HCV disease vs. mixed infiltrate in allograft rejection). Features such as lymphocytic infiltration of the portal tract and variable degrees of bile duct injury with occasional lymphocytic aggregates could be seen in both processes.

To further define the problem, some investigators have suggested the use of tissue HCV RNA levels as a method for distinguishing between ACR and recurrence of HCV infection. Despite considerable overlap between the two groups, a high tissue HCV RNA level favors recurrent HCV infection. Sreekumar et al. performed gene array analysis to differentiate ACR from HCV recurrence and showed a relative over-expression of 25 genes and under-expression 15 genes in ACR that were predominantly associated with major histocompatibility complex groups I and II, tumor necrosis factor-α, complement components, T-cell activation, and apoptosis, suggesting a mechanistic difference between the two processes that could be exploited in diagnosis.

Other investigators found increased interleukin 4 and interleukin 10 gene expression in ACR rather than the interleukin 2/interferon-γ/tumor necrosis factor-α seen in chronic HCV alone.

In general, there are three forms of post-LT HCV disease that need to be recognized: acute recurrence, chronic recurrence, and a rare, primarily cholestatic disease called fibrosing cholestatic hepatitis (FCH).

### Acute Recurrence of Infection

Liver biopsy is characterized by lobular infiltrates, varying degrees of hepatocyte necrosis, and fatty infiltration characteristic of acute HCV infection in the nontransplant population. The enzyme pattern is one of mild to moderately elevated alanine aminotransferase and a total bilirubin below 6 mg/dL.

### Chronic Recurrent HCV Infection

The previously described injury may evolve over time to chronic hepatitis with significant portal and lobular infiltrates, varying degrees of hepatocytes necrosis, and portal-to-portal bridging fibrosis. The immune response in recurrent chronic HCV infection resembles that of chronic HCV infection in the immunocompetent population: a progressive nonspecific TH1 inflammatory response associated with apoptotic and fibrotic pathway involvement.

### Fibrosing Cholestatic Hepatitis

A small percentage of patients (~5%) may present with FCH, a progressive liver injury characterized by jaundice (bilirubin >6 mg/dL) in the absence of biliary or vascular complications, very high serum and intrahepatic HCV RNA levels, serum alkaline phosphatase (>500 U/L) and γ-glutamyl transferase (>1,000 U/L). Serum transaminases will generally be increased by 2 to 5 times the upper limit of normal but can be quite variable. This disorder usually begins by 1 month after LT and may progress over a 3- to 6-month period to liver failure. Histologically, this syndrome is characterized by the presence of severe hepatocyte ballooning (predominantly in the perivenular zone), intrahepatic cholestasis, pericellular and portal fibrosis, ductular proliferation, and paucity of inflammation as the initial manifestation of disease recurrence. The pathogenesis is unknown, but this injury often occurs after high levels of immunosuppression and is believed to represent an alternative response to recurrent HCV infection, as it tends to occur at approximately the same time after LT. This syndrome is associated with stable HCV quasispecies, possibly due to minimal immune pressure, lack of a specific HCV immune response, and increased TGF-β cytokine expression rather than a TH1 response. It seems that FCH represents an immune escape response with consequently high viral burdens. In fact, viral damage in this scenario is more a direct cytotoxic injury to the hepatocytes rather than immune mediated. The course of FCH is inexorably progressive, and attempts at antiviral treatment are generally met with failure.
Risk Factors Associated with Histologic Severity of Recurrence

Most identified factors believed to modulate disease progression in HCV-infected LT recipients remain controversial and are poorly understood. In 2003, the first International Liver Transplantation Society (ILTS) Consensus Panel group for the diagnosis and management of post-LT HCV convened to develop a working classification that categorizes risk factors for recurrence of HCV infection as pretransplantation, posttransplantation, recipient, virological, and other (Table 1).15

Recipient Factors

The Consensus Panel identified increasing recipient age, recipient female gender,22,33 severity of disease prior to liver transplantation, and recipient race (African-Americans, Asian) as well established factors of limited survival. Some other conflicting factors include hepatitis B virus coinfection, coexistence of hepatocellular carcinoma, human immunodeficiency virus coinfection, peritransplantation interferon therapy, HLA-compatibility, and T-cell responsiveness (perhaps the most important host factor).15,22,38,54-56 Unfortunately, some of these factors proposed have not been borne out by large prospective reviews of LT outcomes. For instance, the diagnosis of concomitant HCV infection/HCC had a significant impact on graft and patient survival in a European cohort, whereas a recent analysis of 17,966 patients from the United Network for Organ Sharing data bank did not find a significant difference.57

Donor Factors

The most consistent donor factor associated with fibrosis progression seems to be the use of older donors. Despite efforts to define donor factors that may influence the course of recurrent HCV, only older age has enough evidence to substantiate the claims made by the task force as a significant factor in viral recurrence.26,58 Interestingly, donor infection with HCV has not been linked to poor outcome.59 HLA matching appears to have little effect on the outcome of HCV recurrence. Donor fat content has also been identified as a potential factor.60

Viral Factors

Putative viral risk factors include pre-LT viral load, post-LT viral load, cytomegalovirus infection, viral genotype 1b, and the emergence of quasispecies. Among those, high HCV load (>1 mEq/mL) at transplantation have been consistently shown to predict poor outcomes in HCV-infected recipients.30,38 Despite extensive investigation, neither genotype nor quasispecies variability have been established as a reliable marker of disease recurrence. Elevated post-LT viral titers are a less reliable predictor.8,28,38,59 The influence of cytomegalovirus has recently surfaced as an important factor in progression of disease. This link appears to be stronger if HCV genotype 1a is the infecting viral genotype.61,62

Immunosuppression

The impact of the immunosuppression regimen in the recurrence of HCV infection is a matter of much interest. Berenguer and coworkers have identified the use of stronger immunosuppression as one of the factors contributing to a decreased survival of HCV-positive recipients.26,30 Among all the agents, only the use of steroid boluses and monoclonal antibody preparations (most commonly OKT3) appear to be important factors for the progression of disease.38,61-63 There is no consistent difference between cyclosporine and tacrolimus in their

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### Table 1. Factors Associated With Increased Severity of Recurrent Hepatitis C Infection

<table>
<thead>
<tr>
<th>Factors</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>Recipient related</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>Established (survival)</td>
</tr>
<tr>
<td>Age</td>
<td>Established (survival)</td>
</tr>
<tr>
<td>Nonwhite race</td>
<td>Established (survival, severity)</td>
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<tr>
<td>Severity of illness</td>
<td>Established (survival)</td>
</tr>
<tr>
<td>Donor related</td>
<td></td>
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<tr>
<td>Age</td>
<td>Established (survival, severity)</td>
</tr>
<tr>
<td>Living donor</td>
<td>Controversial (less likely)</td>
</tr>
<tr>
<td>Donor-recipient HLA matching</td>
<td>Controversial</td>
</tr>
<tr>
<td>Genetic</td>
<td>Insufficient data, unknown</td>
</tr>
<tr>
<td>Virological</td>
<td></td>
</tr>
<tr>
<td>Genotype 1b</td>
<td>Controversial (not in United States)</td>
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<tr>
<td>Pretransplant viral load</td>
<td>Established (severity)</td>
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<tr>
<td>Early posttransplant viral load</td>
<td>Established (severity)</td>
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<tr>
<td>CMV infection</td>
<td>Established (severity)</td>
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<tr>
<td>HIV coinfection</td>
<td>Established (severity)</td>
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<tr>
<td>Quasispecies</td>
<td>Controversial</td>
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<tr>
<td>Other</td>
<td></td>
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<tr>
<td>Cold ischemia time</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Time to recurrence</td>
<td>Established (severity)</td>
</tr>
<tr>
<td>Treatment of rejection (OKT3, steroid)</td>
<td>Established (severity)</td>
</tr>
<tr>
<td>Recent transplantation</td>
<td>Established (severity)</td>
</tr>
<tr>
<td></td>
<td>(evidence from Spain)</td>
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Abbreviations: CMV, cytomegalovirus; HIV, human immunodeficiency virus.
effects on HCV.\textsuperscript{64} A very large ongoing multicentric, prospective, randomized controlled trial of tacrolimus, mycophenolate mofetil and daclizumab used in combination to prevent or minimize the use of corticosteroids in this patient population will likely yield major insight on the impact of all these agents on the course of recurrent HCV.

\textbf{Graft}

Several reports have suggested that the recurrence of HCV infection occurs earlier and has a more aggressive course in the living donor liver transplant recipient population compared to the deceased donor liver transplant recipient population. To address this issue, we conducted an analysis of the living donor liver transplant and deceased donor transplant recipient populations at our institution and found no difference in HCV infection recurrence rate or severity by histological analysis at 4 months and 12 months after transplantation between both groups.\textsuperscript{65} A recent update of this analysis at 24 months after transplantation failed to show any histological differences between the groups (L. Guo, communication, February 2005). Other investigators have confirmed this finding in a larger cohort of patients.\textsuperscript{66} Graft ischemia (warm and cold) has been identified as another potential negative factor.\textsuperscript{15}

\textbf{Treatment of Recurrent HCV Infection}

Based on the International Liver Transplantation Society (ILTS) Consensus Panel opinion on post-LT treatment of recurrent HCV infection, and on the available data, there is enough anecdotal and single center reports to suggest that a patient with recurrent HCV infection (and disease) who has stage 2 fibrosis or more should be given a trial of combination therapy with interferon \(\alpha\) and ribavirin.\textsuperscript{15}

Treatment strategies fall into three categories: pretransplantation antiviral therapy, peritransplantation therapy, and posttransplantation therapy. Interestingly, pretransplantation antiviral therapy and posttransplantation therapy (except peritransplantation therapy) seem to yield the same overall rates of virological clearance.\textsuperscript{67} For the purpose of our discussion, sustained virologic response is defined as the absence of detectable HCV RNA by polymerase chain reaction 6 months after discontinuation of antiviral therapy.

\textbf{Pretransplantation}

The goal of HCV treatment in patients with cirrhosis awaiting liver transplantation should be virological clearance.\textsuperscript{65} In fact, most centers today will treat only very well-compensated patients with cirrhosis in the hope that antiviral therapy will eradicate HCV in a proportion of these patients and even delay LT.

The liver transplant group sponsored by the National Institute of Diabetes & Digestive & Kidney Diseases observed that patients with higher pre-LT HCV RNA titers experienced mortality and graft loss rate 30\% more frequently than recipients with a lower pre-LT viral load.\textsuperscript{38} Therefore, it seems reasonable to attempt to treat patients with cirrhosis while waiting for liver transplantation.

Two pilot studies have been conducted in the United States to address this important issue. Crippin and coworkers conducted a pilot trial of pre-LT treatment with interferon \(\alpha\) and ribavirin as decompensated patients with cirrhosis awaited LT (mean Child-Turcotte-Pugh score, 11.9; mean platelet count, 45,000/mm\(^3\)). Unfortunately, very few patients were able to tolerate medications at optimal doses, none of the patients became HCV RNA undetectable, none were able to maintain significant reduction in serum HCV RNA (as was hoped), several patients developed severe infections, and 2 patients died of infectious complications related to treatment. This trial had to be stopped for safety reasons.\textsuperscript{68} A group of investigators from the University of Colorado used a “low accelerating dose regimen” in patients with “stable” cirrhosis (mean Child-Turcotte-Pugh score, 7.1) with significant improvement on tolerance of treatment. Sustained viral response was achieved in 22\% of the patients. Furthermore, those patients who cleared virus preoperatively, remain virus free after LT.\textsuperscript{69} Factors associated with sustained viral response in this study included genotype 2 and 3, and the ability to tolerate full antiviral dose. Taken together, these studies suggest that pre-LT antiviral therapy should be considered only in patients with more compensated liver disease. The ILTS Consensus Panel defined this group of patients as those with a Child-Turcotte-Pugh score of \(\leq 7\) or a Model for End-Stage Liver Disease score of \(\leq 18\). Treatment is not advised for those patients with a Child-Turcotte-Pugh score of \(\geq 11\) or a Model for End-Stage Liver Disease score of \(\geq 25.15,69\)

\textbf{Perioperative Therapy}

Based on the success of hepatitis B immunoglobulin therapy and the observation that HCV/hepatitis B virus–coinfected LT recipients treated with hepatitis immunoglobulin fared better with respect to HCV recurrence than cohorts who did not receive hepatitis C immunoglobulin, several groups have studied the possibility of using pooled serum from patients with demonstrated HCV clearance (hepatitis C immunoglobu-
Limited data is available at this time regarding the efficacy of hepatitis C immunoglobulin preparations to prevent recurrent HCV infection. A randomized controlled study of hepatitis C immunoglobulin for the prevention of post-LT HCV found no benefit in terms of post-LT reinfection rate or HCV RNA levels. Preliminary data with a human anti-E2 immunoglobulin have been somewhat disappointing with low frequency of decline of viral titers. Other clinical trials are currently ongoing. At the moment, there is no clear role for prophylactic therapy with hepatitis C immunoglobulin.

**Posttransplantation**

Two treatment strategies are possible following liver transplantation. The first approach will be the initiation of antiviral therapy as soon as possible after the patients are clinically stable after LT and before histologic recurrence is evident. A second, more selective approach will be the initiation of antiviral therapy in patients with histologic evidence of significant recurrent disease and fibrosis progression. To determine the rate of progression of disease, serial protocol liver biopsies should be performed in this patient population. In our institution, the “threshold” for commencing antiviral therapy after LT is a minimum fibrosis score of 2 of the METAVIR classification system.

Preemptive therapy involves the institution of therapy for HCV as soon as possible after LT based on the assumption that starting antiviral therapy when the viral load is low may enhance viral clearance rate. This approach is based on the observation that treatment of acute HCV infection (nontransplant population) with standard interferon α leads to sustained viral response in over 90% of patients. In the first week after transplantation, serum RNA levels are variable but generally very low. Serum RNA levels peak around 1 to 3 months after transplantation. This viral load peak may correspond to the onset of acute recurrent disease. Unfortunately, the results observed in patients treated in this fashion to date have been disappointing with a sustained viral response between 10% and 25%. The treatment discontinuation rate is as high as 33%. Because of the disappointing results of treatment and lack of formal studies to compare the benefit of this approach, the role of preemptive treatment for the long term remains to be defined.

For the treatment of established disease, a number of trials have investigated the efficacy of therapy with different regimens including standard interferon α monotherapy ribavirin monotherapy, standard interferon α in combination with ribavirin, and lately pegylated interferon α alone or in combination with ribavirin. However, most of these studies are small, single-center reports with significant variability in patient selection, end points (i.e., biochemical response rather than viral response), medication dose, and immunosuppressive approach (Fig. 2).

When evaluating the treatment options, it is important to consider not only the efficacy but also the benefit, safety, and tolerability in this population. Current available options consist of interferon α (either standard or pegylated) with or without ribavirin.

**Interferon α Monotherapy**

Alpha interferon has both direct antiviral activity and immunomodulatory action. The response rate with standard interferon α monotherapy in the treatment of post-LT HCV infection has been disappointing. Despite end-of-treatment response rates (negative HCV RNA immediately at the end of treatment) of 25% to 50%, most will relapse after discontinuation of therapy, and all will be viremic 12 months after discontinuation of therapy. Furthermore, acute and chronic rejection as well as graft loss was reported by some investigators.

**Ribavirin Monotherapy**

Ribavirin’s antiviral mechanisms include depletion of intracellular guanosine triphosphate through the direct inhibition of inosine monophosphate dehydrogenase, interruption of viral messenger-RNA synthesis, and direct inhibition of viral RNA polymerases. It appears to exert an immunomodulatory rather than direct antiviral effect. The proposed mechanism of action is enhancement of HCV-specific T-cell immunity by switching from a predominantly T112 to T111 phenotype.
Four clinical trials have addressed the efficacy of ribavirin monotherapy in the HCV-infected post-LT population. Other than improving the level of transaminases and possibly reducing lobular fibrosis, ribavirin has not had much success either in terms of virological response or progression of fibrosis.\(^78,80,83-85\)

**Combination Therapy With Standard or Pegylated Interferon α and Ribavirin**

The synergistic effect from the combination of interferon α with ribavirin results in much better response rates in the immunocompetent population and in the posttransplantation population. The later addition of multiple polyethylene glycol moieties to standard interferon α (pegylated interferon α) have resulted in a much larger molecule with a reduced volume of distribution, a longer half-life, and an increased antiviral efficacy. Nevertheless, combination therapy is marginally tolerated in the post-LT population, with a reported sustained virological response of 9% to 45% compared with the nontransplant HCV population.\(^86-88\)

In an intention-to-treat analysis, we found a 37% end-of-treatment response rate to therapy with combination pegylated interferon alpha 2b and ribavirin when using a treatment-on-recurrence strategy. More importantly, 26% of the patients went on to have a sustained viral response. The histological response to treatment by patients who completed 48 weeks of therapy revealed no statistically significant alteration in the mean fibrosis stage, but the fibrosis score improved in 60% of sustained responders, remained unchanged in 20%, and progressed in 20%. Comparison of paired liver biopsies (pretreatment/posttreatment) revealed that the overall mean inflammation in the sustained responders group and in the nonresponders group improved.\(^86\) A 2-year follow-up histological analysis of the same cohort of patients demonstrated a histological improvement among those with sustained viral response with an improvement in stage of 1.85 vs. 2.3 for nonresponders (personal communication). In a similar study, Dumortier et al. found a sustained viral response of 45% with a similar protocol.\(^89\) In another study, Neff et al. reported a 27% end of treatment response, however no data on sustained viral response was reported.\(^90\)

Treatment of recurrent HCV infection is cumbersome and complicated by the lower patient tolerability necessitating frequent dose adjustment, adjuvant hematopoietic/leukopoietic agents, and, oftentimes, treatment discontinuation. Approximately 30% to 60% of the treated patients require ribavirin dose reduction, and 30% need discontinuation of therapy for myriad reasons, including depression (−10% of patients).\(^86,91\) To date, there is no compelling evidence that interferon α increases the risk of acute or chronic cellular rejection.

The duration of therapy is uncertain, as there are neither good post-LT trials showing that 12 months of treatment are more effective than 6 months, nor studies showing clearly that a failure of virological response at 3 months of treatment predicts a lack of longer-term response. However, it makes sense to treat this immunosuppressed population for a full 12-month period, if tolerated, as the transplant population with recurrent HCV infection possesses multiple baseline risk factors that impact negatively the natural history of HCV. The case of FCH is a more complicated one, and some investigators, such as Rosen et al., have suggested long-term antiviral therapy for this population.\(^92\)

Finally, Saab et al. conducted a cost-effectiveness analysis of treatment with combination standard interferon α plus ribavirin and found an incremental cost-effectiveness ratio of $29,100 per life-year saved for men aged 55 years. The model was sensitive to drug costs, cirrhosis rate, and sustained viral response. The two-way sensitivity analysis showed that antiviral therapy remained cost-effective even if drug costs increased, as long as these increases were associated with higher sustained viral responses.\(^93\)

The potential benefit for long-term antiviral maintenance therapy, either normal-dose or low-dose interferon α with or without ribavirin, in patients with recurrent HCV disease is not recommended and should be pursued only in the context of clinical trials.\(^15,67,91\)

**Management of Treatment Side Effects**

This population seems to tolerate therapy less well than immunocompetent chronic HCV-infected patients. Approximately 30% to 60% of the patients require dose reduction, and 30% discontinuation because of hemolysis vs. less than 10% and 2% of nontransplant patients, respectively. Depression may lead to discontinuation of therapy in approximately 10% of the patients. Recommendations to control some of the complications include:

- **Anemia:** Start erythropoietin upon decrease in hemoglobin below 3 g/dL from baseline or upon symptomatic anemia at a dose of 40,000 units weekly (or twice a week) until hematocrit reaches 36% or upon reaching patient’s baseline hemoglobin. Decrease ribavirin dose by 50% if no response, and consider discontinuation if desired hemoglobin increase not achieved.
Neutropenia: Start G-CSF upon decrease of absolute neutrophil count below 1,000 cells/mL at a dose of 5 μg/kg once (or twice a week) until resolution. Consider interferon dose reduction.

Worsening hepatic function: Discontinue treatment, and consider liver biopsy to rule out other causes. Consider long-term treatment if FCH variant.

Rejection: Discontinue treatment (permanently).

Infections: Discontinue treatment (may restart after resolution of infection).

Psychiatric disturbances: Institute antidepressants, preferably under psychiatric supervision. Selective serotonin reuptake antagonists can be used with success. Consider interferon α dose reduction or discontinuation until resolution or stabilization of disturbance.

Despite these side effects, treatment of recurrent HCV infection should be offered to post-LT patients with histological evidence of aggressive recurrence of disease given the benefit of therapy.

Retransplantation

Retransplantation for recurrent HCV-associated graft failure represents a challenge and is plagued with ethical and nonethical issues ranging from utilization of a scarce resource to survival. There is a growing concern that rapid recurrence of HCV infection and accelerated fibrosis may lead to a large number of patients requiring retransplantation. At the present time, liver transplantation for this indication accounts for approximately 2% to 3% (annually) in the United States.24 Two well-accepted indications for retransplantation in a patient with HCV are graft failure unrelated to HCV infection (primary nonfunction, hepatic artery thrombosis, etc.) and graft failure from rapidly progressive fibrosis secondary to HCV infection. Survival of these patients is similar to that observed for non-HCV disease.95

Previous studies have shown that survival after retransplantation is excellent (80% 2-year survival) when performed on a nonurgent basis in patients with relatively stable liver and renal function in contrast to ∼40% when performed in patients with decompensated liver disease and renal failure.96-100 Risk factors associated with “worse” retransplantation outcome include total bilirubin over 10 mg/dL, creatinine level over 2.0 mg/dL, creatinine clearance of less than 40 mL/min, recipient age over 55 years, early recurrence with development of cirrhosis at less than 1 year, and donor age over 40 years.15,95 It appears that retransplantation in the setting of rapidly recurrent HCV infection is a matter of timing and should be considered early after identification of the process.

Summary

HCV-related cirrhosis is still a valid indication for LT, despite the frequency of recurrence. As this segment of the LT-recipient population grows, the transplantation hepatologist needs to consider the challenge of preventing aggressive recurrence and considering the value of retransplantation in this patient group. Current treatment options for HCV offer limited chance of long-term success. There is ample room for investigation into the most beneficial regimen and duration of treatment, the time at which one should start, and how all the factors over which the clinician and patient have control will be manipulated to achieve the highest possible disease- and symptom-free survival.

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