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Minireview

Management of Hepatitis C in Liver Transplant Recipients

A. Kuo and N. A. Terrault*

Division of Gastroenterology, University of California San Francisco, San Francisco, CA, USA
**Corresponding author: N. A. Terrault, Norah.Terrault@itsa.ucsf.edu*

Recurrent hepatitis C virus (HCV) disease is the leading cause of graft loss in liver transplant recipients with pre-transplant HCV infection. While natural history is variable, median time to recurrent cirrhosis is less than a decade. Factors contributing to risk of recurrence and rate of fibrosis progression are only partially known. Older donor age, treatment of acute rejection, cytomegalovirus infection and high pre-transplant viral load are most consistently linked with worse outcomes. Whether these factors can be modified to positively impact on HCV disease progression is unknown. The main therapeutic approach for patients with recurrent HCV disease has been the treatment with interferon and ribavirin (RBV) once recurrent disease is documented or progressive. Efficacy is lower than in nontransplant patients and tolerability, especially of RBV, is a major limitation. Stable or improved fibrosis scores are seen in the majority of sustained responders. Optimal dose, duration and timing of treatment have not been determined. Alternative strategies under study include pre-transplant treatment of decompensated cirrhotics, preemptive antiviral therapy started within weeks of transplantation and prophylactic therapy using HCV antibodies. Ongoing studies may establish a future role for alternative treatment approaches. Additionally, limited overall efficacy of interferon-based therapy in the transplant setting highlights the urgent need for new drug therapies.

Key words: Cirrhosis, hepatitis C immunoglobulin, immunosuppression, pegylated interferon, ribavirin

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Introduction

End-stage liver disease caused by chronic hepatitis C virus (HCV) infection is the most common indication for liver transplantation in the United States and Western Europe. Following liver transplantation, graft reinfection with HCV is essentially universal and the rate of fibrosis progression is accelerated as compared to immunocompetent patients with HCV. Recurrent disease affects long-term graft survival. Patients with HCV-related liver disease have a 23% increased rate of mortality and a 30% increased rate of graft loss at 5 years post-transplantation as compared to patients transplanted for other indications (1). Cirrhosis is reported in up to 30% of recipients within 5 years (2), and progression is not linear (3). Once cirrhosis is established, patients are at high risk for complications, with up to 42% developing liver decompensation within 1 year (4). Retransplantation, the only definitive therapy for recurrent disease with decompensation, is controversial in patients with HCV, as their survival is inferior compared to patients with non-HCV indications (5,6).

Given the limited availability of donor organs and the tremendous resources invested into each liver transplant recipient, strategies to maintain the long-term survival of HCV-infected patients are of paramount importance. An improved understanding of the host, viral and external factors influencing HCV disease recurrence is essential, as some factors may be modifiable. Therapeutic interventions undertaken prior to or after transplantation represent an important means of preventing infection or modify the risk of progressive HCV disease.

Factors Influencing the Natural History of Recurrent HCV Disease

Recurrent HCV disease has a variable onset and rate of progression. The factors most consistently associated with severe recurrent HCV disease, defined by more rapid progression to fibrosis or cirrhosis, were donor age, cytomegalovirus (CMV) infection and treatment of acute rejection (use of steroid pulses or anti-lymphocyte therapies such as OKT3) and pre-transplant HCV viral load (2,3,7–12). Not surprisingly, factors associated with graft loss overlap with those predicting HCV disease severity (Table 1).

Several studies have reported older donor age to be a risk factor for premature graft loss and death (3,8,9,13). A recent report suggests that the risk of premature graft loss begins with donors 40 years of age and higher, with hazard ratios for graft loss of 1.67 (95% CI: 1.34–2.09) with donors 41–50 years, 1.86 (95% CI: 1.48–2.34), for donors 51–60 years, and 2.21 (95% CI: 1.73–2.81) for donors >60 years of age (9). CMV is associated with more severe

Table 1: Factors associated with HCV disease severity and graft loss

Factor	Associated with HCV disease severity	Associated with graft survival	Specifics
Recipient-related			
Female gender		X	
Older age		X	
Non-White race		X	
Severe pre-transplant liver disease		X	Sicker patients have reduced survival
Transplant-related			
Older donor age	X	X	Increased risk with donor age >40 years
Treatment of rejection	X	X	Use of corticosteroid boluses and OKT3 linked with severity
CMV infection	X		
Time to recurrence	X		Early recurrence predictive more severe disease
Viral factors			
High pre-transplant HCV viral load	X	X	The specific cutoff has not been defined prospectively

Adapted from ILTS Expert Panel on Liver Transplantation and Hepatitis C, Liver Transplant 2003; 9 (suppl 3): S1–S9.

HCV disease and although the underlying mechanism is uncertain, the effect appears to be independent of treatment of acute rejection (8,14). High pre-transplant viral load has been associated with worse clinical outcomes. In a multicenter cohort study, high HCV RNA levels at transplantation were associated with greater risk of progressive HCV disease, but HCV quantitation methods were not standardized in this study (2). In the NIDDK-LTD, a pre-transplant HCV viral load greater than 10^6 copies/mL was associated with decreased graft and patient survival, but the relationship of the viral load to liver histology was not assessed (15).

Treatment of acute rejection with steroid pulses or anti-lymphocyte therapies has been associated with higher risk of cirrhosis and fibrosis progression (3,11,12,16). The diagnosis of acute rejection in the presence of coexistent recurrent HCV can be difficult, and new diagnostic tools to help differentiate between HCV and HCV plus rejection are needed. The International Liver Transplantation Society (ILTS) Consensus statement highlighted the need to weigh carefully the treatment of mild rejection with the potential detrimental effects of corticosteroid boluses and lymphocyte-depleting agents on HCV (7).

Whether donor status (live vs. deceased) influences HCV disease progression is a controversial issue. Theoretically, rapidly proliferating hepatocytes and an altered cytokine milieu in the regenerating graft may affect HCV replication and early immunological events such that the risk of disease progression is affected. In a Spanish study comparing histological severity of disease on protocol biopsies, the 2-year probability of developing cirrhosis or clinically decompensated liver disease was 22% in deceased donor recipients versus 45% in living donor recipients ($p = 0.019$) (17). The unusually high rate of cirrhosis raised concerns regarding the generalizability of the findings. A U.S. study that used protocol liver biopsies to assess disease severity reported very different results. At 36 months post-transplantation, there was no evidence of worse histology in 23 living donor recipients compared to 53 deceased donor recipients, with bridging fibrosis in 12% versus 39%, respectively, and there were no cases of cirrhosis in either group (18). Additionally, a recently published analysis of graft survival using United Network for Organ Sharing (UNOS) data between 1999–2003, found no increased risk of death in patients with HCV who underwent living donor transplants as compared to deceased donor transplants (19).

Other controversial risk factors include, HCV viral genotype, donor–recipient HLA matching, cold ischemia time and the effect of specific immunosuppressive agents (7). While immunosuppression is presumably central to the more accelerated course of HCV disease post-transplantation, little is known about how to modify immunosuppression in order to minimize the rate of HCV disease progression. Given the negative effect of acute rejection treatment on HCV disease progression and graft survival, prevention of acute rejection is of prime importance. On the other hand, this goal must be balanced with the risks of excessive immunosuppression that may negatively impact on HCV infection. Interpretation of available studies is hampered by a lack of histological endpoints and dependence of graft survival as an outcome; the routine use of drug combinations which makes the evaluation of a specific drug effect more complex; and the confounding effects of differential rates of acute rejection in treatment groups.

Specific immunosuppressive drugs and HCV disease severity

Use of corticosteroid pulses and anti-lymphocyte therapies have been consistently implicated as detrimental to HCV disease, but these drugs are given in the setting of acute rejection (3,11,12,16). Whether lymphocyte-depleting drugs, when used as induction therapy, have a negative effect on HCV disease progression is less clear. A prospective randomized trial of rabbit anti-thymocyte globulin (ATG) followed by tacrolimus plus mycophenolate mofetil (MMF) versus tacrolimus, MMF and corticosteroids (boluses followed by prednisone taper) showed no differences in

the rates of graft survival, recurrent HCV disease, fibrosis or HCV RNA levels at 1 year post-transplantation (20). In contrast, a retrospective cohort of transplant patients with HCV receiving pre-treatment with alemtuzumab, reported elevated HCV RNA levels post-infusion and higher rates of recurrent HCV within 1 year post-transplantation (21). These divergent results may be due to the different lymphocyte depleting drugs used, the rate of withdrawal of other immunosuppressive drugs, or other unmeasured donor or recipients factors affecting the risk of HCV recurrence. Pending additional studies, caution in the use of potent lymphocyte-depleting therapies appears warranted.

Cyclosporine appears to have viral suppressive effects *in vitro* (22), but in liver transplant recipients with HCV, no significant difference in HCV RNA levels was evident in cyclosporine-treated versus tacrolimus-treated patients (23). Additionally, in prospective studies comparing the two different calcineurin inhibitors, there is not significant difference in HCV disease severity or risk of cirrhosis between groups (23–25). There has been ongoing interest in the effect on MMF on HCV recurrence and severity due to its structural homology to ribavirin (RBV). No consistent effect (positive or negative) on HCV histology and risk of cirrhosis has been established (26,27).

Steroid boluses used to treat acute rejection are associated with an increase in HCV viral loads (28), and concerns regarding the potential negative effects of corticosteroids in HCV-infected patients prompted evaluation of steroid-free regimens and alternative protocols of steroid withdrawal (20,29–31). Since steroid-free regimens frequently use anti-interleukin-2 receptor antibodies or lymphocyte-depleting agents also, the independent contribution of steroid elimination and use of lymphocyte-depleting drugs can be difficult to discern (20,30). Both steroid-free immunosuppression and early withdrawal of corticosteroids may reduce the risk of metabolic complications (20,30), but no clear benefit on HCV disease progression has been demonstrated. Both the rate and timing of steroid withdrawal have been proposed to be of importance but the available data are not strong enough to support any one specific corticosteroid tapering protocol (29,31).

Prevention and Treatment of Recurrent HCV Disease

To *prevent* recurrent HCV disease, treatment must be initiated prior to or at the time of transplantation and continued post-transplantation in a prophylactic fashion. If pre-transplant and prophylactic therapies are unsuccessful and recurrent infection develops, post-transplant *treatment* can be administered prior to the development of overt clinical disease (preemptive therapy) or after histological progression is evident. In the post-transplant setting, the goals of therapy are two-fold. Viral eradication is the primary goal, but slowing disease progression is equally important in those unable to achieve viral clearance. Among those patients who achieve sustained virologic responses (SVRs), uniform improvements in histology are not seen in all patients. A U.S. study of 29 transplant patients with an SVR and mean 2 years follow-up after treatment reported the fibrosis stage was improved in 67%, unchanged in 13% and worsened in 20% (32). A French study of 34 patients with SVR (2 with late virologic relapse) found 44% of patients had a stable fibrosis score over a mean 52 months follow-up post-treatment, 38% had improved fibrosis scores and 18% worsened whereas the fibrosis scores in nonresponders worsened in 74% (33). These studies indicate histological benefits are achievable in the majority of patients who have an SVR.

At present, the only drugs available for treatment of recurrent disease in transplant recipients are interferon (conventional and pegylated forms) and RBV. Antiviral treatment of recurrent HCV disease is hampered by a high prevalence of genotype 1 in transplant patients, the reduced efficacy of IFN in the setting of immunosuppression, and a higher rate of complications especially cytopenias. Additionally, there is a theoretical risk of triggering acute rejection with use of interferon. In uncontrolled studies, the rate of rejection with 48 weeks of interferon and RBV therapy range from 0–30%, but with the majority of studies reporting acute rejection in $\leq$10% of treated patients (32,34–40). Factors potentially influencing the risk of rejection include the level of immunosuppression at the time of treatment initiation, the type of interferon used (more potent pegylated interferons potentially being higher risk for rejection), whether RBV was used (possibly immune modulatory effects) and whether the patient had prior problems with rejection. Controlled studies have found no differences in acute rejection rates between treated patients and untreated controls (41,42).

Pre-transplantation HCV treatment

The rationale for pre-transplant HCV treatment is that viral eradication prior to organ implantation will prevent or reduce the risk of recurrent infection post-transplantation. Whether reduction in HCV viral load without eradication leads to attenuation of HCV disease severity requires further study. An estimated 17–25% of patients with cirrhosis or advanced fibrosis may be eligible for pre-transplant antiviral therapy (43).

In nontransplant HCV patients, treatment with combination therapy using pegylated interferon (peg-IFN) and RBV achieves an SVR in 42–46% of patients with genotype 1 and 76–80% of patients with genotypes 2 and 3 (44,45). In pre-transplant patients with decompensated liver disease, the efficacy rates are diminished and the frequency of side effects are increased (Table 2). In a treatment protocol using a low ascending dose regimen of

Table 2: Studies of pre-transplant HCV treatment in patients with decompensated cirrhosis

Study	Regimen Pts	(# pts)	Duration	Virological response	Rate of HCV recurrence	Complications
Crippin 2002 (47)	15	(i) IFN 1 MU QD (3) (ii) IFN 3 MU TIW (6) (iii) IFN 1 MU QD and RBV 400 mg BID (6)	8 weeks (mean)	33% EOTVR	2/2 (100%)	13/15 pts with AEs 20/23 AEs were severe (2 serious infections, including 1 death)
Thomas, 2003 (67)	20	IFN 5 MU QD (20)	14 weeks (mean)	60% EOTVR	8/12 (67%)	Excluded pts with platelets <50 K. 3/20 terminated early, 3/20 interrupted for thrombocytopenia. All required G-CSF at some point in Rx.
Forns 2003 (46)	30	IFN 3 MU QD and RBV 800 mg QD	12 weeks (median)	30% EOTVR	3/9 (33%)	20% early d/c therapy 63% any dose reduction (60% IFN, 23% RBV)
Everson 2003 (43)	124	*IFN 1.5 MU TIW and RBV 600 mg QD *IFN increased to 3 MU TIW at week 2 *RBV increased by 200 mg weekly after week 4	Not reported	24% SVR	3/15 (20%)	12% liver-related complications

IFN = interferon; RBV = ribavirin; MU = million units; QD = once daily; BID = twice daily; TIW = thrice weekly; EOTVR = end of treatment virologic response (undetectable HCV RNA by PCR); G-CSF = granulocyte colony stimulating factor; SVR = sustained virologic response (undetectable HCV RNA 6 months after completion of therapy).
*Goal of IFN 3 MU TIW and RBV 1–1.2 g/day.

conventional IFN and RBV (target doses: IFN 3 MU thrice weekly and RBV 1–1.2 g/day), SVR was achieved in 24% overall, with higher responses in those with non-1 genotypes (50%) compared to those with genotype 1 (13%) (43). Fifteen patients achieving SVR were eventually transplanted and 12 (80%) were without evidence of HCV recurrence post-transplantation. In contrast, all of the 32 nonresponders/relapsers who were transplanted developed recurrent HCV. Thus, achievement of SVR prior to transplantation reduces the risk of HCV recurrence post-transplantation.

In a similar study, 30 patients with HCV cirrhosis awaiting liver transplantation (50% Child's class B and C) were treated with standard IFN 3 MU daily and RBV 800 mg/day for a median of 12 weeks (46) (Table 2). End of treatment virologic responses (EOTVR) were achieved in 9 (30%) patients and 6 (66%) remained HCV RNA negative following transplantation. This suggests that an on-treatment virologic response (without SVR) may be sufficient to prevent HCV recurrence post-transplantation in some patients.

Tolerability of therapy is dependent upon the severity of liver disease; patients with more advanced liver disease experience a higher rate of adverse events (Table 2) (47). In a randomized study of 15 Child's class B or C cirrhotic patients, 13 patients experienced adverse events and 20 of the 23 adverse events were graded as severe, causing the study to be terminated early. The authors concluded that patients with advanced liver disease are not candidates for antiviral therapy.

The optimal therapy in patients with decompensated cirrhosis has not been defined. There have been no randomized trials comparing standard IFN versus peg-IFN in patients with decompensated cirrhosis. Although a peg-IFN regimen may result in higher rates of SVR, it may come at the price of a potentially greater risk of side effects, especially cytopenias (44,45,48). The presence of hypersplenism resulting in lower baseline cell counts will increase the risk of cytopenias during IFN and RBV therapy. Additionally, renal dysfunction related to drug therapy or underlying liver disease may affect RBV clearance and lead to heightened risk of anemia. Growth factors, to correct anemia and neutropenia, have not been formally studied in patients with decompensated cirrhosis, but minimizing drug discontinuations is desirable in order to enhance SVR rates. Thus, in a population at heightened risk of cytopenias, use of these adjuvant therapies may be particularly beneficial. Growth factor use was supported by the ILTS Expert Consensus Panel on Liver Transplantation and Hepatitis C (7). Management of thrombocytopenia remains problematic, as safe and uniformly effective thrombopoietic drugs are not available.

The enthusiasm for treating patients with antiviral therapy pre-transplantation stems from the desire to reduce

or eliminate the risk of recurrent HCV disease. Results to date indicate that attainment of SVR prior to transplantation can prevent recurrent HCV post-transplantation and an undetectable viral load on treatment (in absence of SVR) may be sufficient in some patients to prevent post-transplant recurrence. However, tolerability of these drugs is limited in patients with advanced decompensated disease. At this time, the routine treatment of patients with decompensated cirrhosis cannot be recommended outside of clinical trials. In particular, the risk–benefit of antiviral treatment in patients with genotype 1 is unclear, since SVR rates are <20% in these patients. A National Institutes of Health (NIH) sponsored multi-center trial investigating the efficacy and safety of a low ascending dose regimen of peg-IFN alfa 2b plus RBV in HCV infected patients listed for transplant with a potential living donor is underway. Since patients undergoing adult living donor transplants generally have less severe disease than patients who undergo deceased donor transplants, this group of patients may be best able to tolerate antiviral therapy pre-transplantation.

Post-transplantation HCV prophylaxis with hepatitis C antibody therapy

Isolate specific neutralizing antibodies to HCV have been demonstrated and these antibody responses correlate inversely with HCV RNA levels in acutely infected individuals (49,50). Krawczynski et al. studied the effect of post-exposure prophylaxis with hepatitis C immune globulin (HCIG) in chimpanzees and found HCIG delayed the development of acute hepatitis but did not uniformly prevent HCV infection (51).

Two phase II clinical trials investigating the efficacy of HCIG in the prevention of HCV infection in liver transplant patients have been completed (52,53) but only one published (52). The results have been disappointing. In the study testing HCIG (Civacir®, Nabi Biopharmaceuticals, Boca Raton, FL) at doses of 75 mg/kg and 200 mg/kg, transient decreases in liver HCV RNA levels and lower serum aminotransferase levels were seen in patients receiving the highest dose of HCIG. However, these changes were not sustained off treatment and infection was not prevented (52).

Currently there is no role for HCV antibody therapy in the management of HCV patients post-transplantation. Whether an HCIG product with a higher titer of neutralizing antibodies would be more effective in preventing HCV infection is unknown. Both a reliable assay to measure neutralizing antibodies and an improved understanding of the humoral response in acute HCV infection are needed to guide future studies of antibody therapy. Monoclonal antibodies directed against epitopes in the envelope regions of HCV (XTL-Ab65 and XTL-AB68, XTL Biopharmaceuticals, Rehovet, Israel) are being studied in transplant patients. (HCIG (Civacir®) received orphan drug status in Europe in June 2005.)

Post-transplantation preemptive HCV treatment

Treating HCV in the early post-transplant period holds several theoretical advantages. Low viral loads immediately post-transplant may lead to higher rates of SVR. The lack of advanced fibrosis or cirrhosis in the graft could also improve both efficacy and tolerability. However, the higher doses of immunosuppression in the early post-transplant period may reduce the likelihood of response and presence of cytopenias and other complications may limit tolerability of IFN and RBV.

Preemptive anti-HCV treatment has been used with variable success and tolerability (Table 3). Only 40% of patients will be both clinically stable and have sufficient cell counts to begin antiviral therapy within the first 1–2 months post-transplantation (54). Earlier studies of IFN monotherapy achieved EOTVR in only 0–17% of treated patients and SVRs were not seen (55,56). A recent study of Peg-IFN monotherapy (135 ug/week) started within 3 weeks of transplantation achieved an SVR in only 8% (42). Shergill et al. randomized patients within 2–6 weeks of transplantation to IFN alfa-2b or peg-IFN alfa-2b (3 MU thrice weekly or 1.5 mcg/kg per week) versus IFN or peg-IFN plus RBV (600 mg increased to 1000–1200 mg/day) for a total of 48 weeks (54). Dose reductions were required in 85% of patients and therapy was discontinued in 41%, despite the use of growth factors. EOTVR and SVR occurred in only 14% and 9%, respectively, with SVRs more frequent in those receiving combination therapy. In contrast to these U.S. studies, Suguwara et al. reported an SVR rate of 39% among 23 HCV-infected live donor recipients treated with IFN 3 MU thrice weekly and RBV 400 mg/day begun within 1 month of transplantation and continued for 48 weeks (57). There was a significantly less histologic activity in the treated group compared to the nontreated group. Dose reductions or early discontinuation of therapy occurred in 57% of patients.

Several conclusions can be drawn from these studies. The SVR rates of IFN monotherapy are low and range from 0–17%. The addition of RBV appears to increase the SVR rate to 9–39% with the best results in patients with nongenotype 1 disease and in living donor recipients. Overall, tolerability of antiviral therapy is poor with dose modifications are required in >50% of treated patients. Clearly, the availability of more effective and better-tolerated antiviral agents would make preemptive therapy a more attractive treatment strategy.

Post-transplant recurrent HCV treatment

Rather than using antiviral therapy preemptively, most clinicians wait until there is histological evidence of recurrent HCV disease. Controlled trials on antiviral therapy are limited; most of the available data come from single-center uncontrolled studies of small sample size (58). Nonetheless, results are consistent in showing that combination therapy is superior to IFN monotherapy, and that treatment tolerability is a major issue.

Table 3: Studies of post-transplant preemptive HCV treatment

Study	Pts #	Regimen (# pts)	Duration	Virological response	Histological response	Dose reduction or discontinuation
Interferon monotherapy						
Singh 1998 (55)	24	(i) IFN 3 MU TIW (12) (ii) No treatment (12)	24 weeks	No difference	Recurrent hepatitis: (i) 50% (ii) 42%	Not reported
Sheiner 1998 (56)	71	(i) IFN 3 MU TIW (30) (ii) No treatment (41)	1 year	EOTVR: (i) 16.6% (ii) 5.2%	Recurrent hepatitis: (i) 8 of 30 (26.7%) (ii) 22 of 41 (53.7%)	27% early d/c
Pegylated interferon monotherapy						
Chalasani 2005 (42)	54	(i) Peg-IFN 180 mcg Qwk (26) (ii) No treatment (28)	48 weeks	SVR: (i) 8% (ii) 0%	No statistical difference in HAI or fibrosis	31% early d/c
Interferon and ribavirin combination therapy						
Shergill 2004 (54)	44	(i) IFN 3 MU TIW or peg-IFN 1.5 mcg/kg Qwk (22) (ii) IFN or peg-IFN and RBV 600–1200 mg QD (22)	48 weeks	SVR: (i) 2.5% (ii) 18%	70% stage 0. 20% stage 1. No difference in fibrosis between groups	Dose reduction or early d/c: (i) 85% (ii) 37%
Sugavara 2004 (57)	23*	IFN and RBV	12 months	SVR: 39%	Improved HAI score at 1 year in treated patients	Dose modification or discontinuation in 57%

IFN = interferon; RBV = ribavirin; MU = million units; QD = once daily; TIW = thrice weekly; EOTVR = end of treatment virologic response (undetectable HCV RNA by PCR); SVR = sustained virologic response (undetectable HCV RNA 6 months after completion of therapy); HAI = histologic activity index.
*Living donor liver transplant recipients.

Monotherapy with either interferon or peg-IFN has shown low SVR rates, ranging from 0–12% (42,59,60). Combination therapy with standard interferon and RBV yields higher SVR rates (40,41,61–65) (Table 4). In the only controlled study of combination therapy, Samuel et al. treated 28 patients with recurrent HCV with IFN 3 MU thrice weekly and RBV 800–1000 mg/day for 48 weeks (41). The SVR rate was 21% of treated patients versus 0% in controls. In this study, no difference in histology was apparent between groups at 6 months post-treatment. Other studies report improvements in necroinflammation but less consistent improvements in fibrosis scores, the latter possibly related to the stage of fibrosis at the initiation of therapy, with more advanced stages being less reversible, and to the timing of biopsy in relationship to completion of therapy. Improvements in fibrosis would be expected to lag behind virologic and biochemical responses.

In an effort to improve virologic response rates, combination regimens with peg-IFN and RBV are now being used (Table 4). Neff et al. reported an EOTVR rate of 21–28% after treatment with peg-IFN 1.5 mcg/kg per week and RBV 400–600 mg QD for 48 weeks (66). Using a lower dose of peg-IFN and a higher dose of RBV, Dumortier et al. demonstrated an SVR rate of 45% with associated improvements in both inflammation and fibrosis (36). Studies of larger sample size are needed to establish SVR rates and predictors of response. Given the greater efficacy of peg-IFN over standard IFN in nontransplant settings, peg-IFN based combination therapy with RBV would be predicted to be the best therapy for recurrent HCV post-transplantation.

Tolerability of treatment remains a major limitation, even when used in stable patients several years from the time of transplantation. Dose reductions or drug discontinuation due to adverse effects are frequent, especially for RBV. Knowledge of the kinetics of RBV in transplant recipients would be helpful in optimizing dosing. RBV pharmacokinetics are influenced by renal function, and renal dysfunction related to calcineurin inhibitor use is not uncommon in transplant recipients. Maximum RBV doses achieved in studies to date are typically 200–600 mg lower than target doses used in nontransplant populations. Given the frequent complication of anemia and leukopenia during anti-HCV treatment, growth factors are usually needed. However, controlled studies establishing the benefits of adjuvant growth factor use in achieving improved tolerability, fewer dose reductions, or improved SVR rates are lacking.

Summary and Future Directions

The need to prevent or curb the progression of HCV disease post-transplantation is tremendous. Prevention of recurrence occurs when HCV is eradicated prior to transplantation. While SVR prior to transplantation is the goal, the attainment of an on-treatment virologic response appears to prevent HCV recurrence, at least in a proportion of

Table 4: Studies of post-transplant recurrent HCV treatment*

Study	Pts #	Regimen (Pts #)	Duration	Virological response	Histological response	Dose reduction or discontinuation
Interferon monotherapy						
Gane 1998 (59)	30	(i) IFN 3 MU TIW (14) (ii) RBV up to 1.2 g QD (16)	24 weeks	HCV RNA remained detectable by PCR	No improvement in HAI in either group	(i) 21% dose reduction (ii) 25% early d/c due to hemolysis
Pegylated interferon monotherapy						
Chalasani 2005 (42)	67	(i) Peg-IFN 180 mcg Qwk (34) (ii) No treatment (33)	48 weeks	SVR: (i) 12% (ii) 0%	No significant difference in HAI or fibrosis	30% early d/c
Interferon and ribavirin combination therapy						
Firpi 2002 (40)	54	IFN 3 MU TIW and RBV 800–1000 mg QD	12 months	SVR: 30%	No progression of fibrosis in pts with SVR	72% dose reduction
Samuel 2003	52	(i) IFN 3 MU TIW and RBV 800–1200 mg QD (28) (ii) No treatment (24)	12 months	EOTVR: (i) 32% (ii) 0% SVR: (i) 21% (ii) 0%	No significant difference in inflammation or fibrosis	43% early d/c
Bizollon 2003 (63)	54	IFN 3 MU TIW and RBV 1000 mg QD × 6 months; then RBV × 12 months	6 months + 12 months	SVR: 26%	12/14 with SVR had improved Knodell score but no change in fibrosis	11% early d/c of RBV
Giostra 2004 (61)	31	RBV 10 mg/kg QD × 12 weeks; then RBV and IFN 3 MU TIW	Up to 60 weeks	SVR: 29%	Decreased inflammation but no change in fibrosis	77% early d/c opr dose reductions (RBVC much INF)
Berenguer 2004 (64)	24	IFN 1.5–3 MU TIW and RBV 600–1200 mg QD × 12 months; then RBV × 6 months	12 months + 6 months	SVR: 12.5%	No significant difference in inflammation or fibrosis	29% early d/c 88% dose reduction
Mukherjee 2005 (62)	38	IFN 3 MU TIW and RBV 1000–1200 mg QD	12 months (genotype 1) 6 months (others)	SVR: 26%	No change in fibrosis	37% early d/c
Pegylated interferon and ribavirin combination therapy						
Neff 2004 (66)	57	Peg-IFN 1.5 mcg/kg/week and RBV 400–600 mg QD	48 weeks	EOTVR: 27.6% IFN naïve 21% previous nonresponders	Not reported	39–45% RBV dose reduction
Dumortier 2004 (36)	20	Peg-IFN 0.5–1 mcg/kg/week and RBV 400–1200 mg QD	12 months	SVR: 45%	Improved inflammation and fibrosis	20% early d/c dose reduction: 30% IFN 64% RBV

*Limited to studies of at least 20 treated patients.

IFN = interferon; RBV = ribavirin; MU = million units; QD = once daily; TIW = thrice weekly; d/c: discontinuation; EOTVR = end of treatment virologic response (undetectable HCV RNA by PCR); SVR = sustained virologic response (undetectable HCV RNA 6 months after completion of therapy); HAI = histologic activity index.

treated patients. Unfortunately, SVR and on-treatment virologic responses are achievable in <50% of treated patients with decompensated cirrhosis, and response rates in patients with genotype 1 are low. Moreover, the majority of patients on the waiting list are not candidates for antiviral therapy, as tolerability is poor in those with advanced liver disease (Child's class B and C) is poorly tolerated. Post-transplant prophylaxis with HCV antibody therapy has been disappointing and despite the recent approval of Civacir® as an orphan drug in Europe, HCV antibody therapy has no established role in the transplant setting. Preemptive treatment in the early post-transplant period is hampered by poor tolerability of IFN-based therapy in patients recently transplanted, though recipients of living donor organs may be better suited to undertake treatment early. Post-transplant treatment of recurrent HCV currently offers the greatest efficacy and best safety profile at the present time, though many patients do not achieve viral eradication with standard treatment regimes. Pegylated interferon plus RBV has emerged as the therapy of choice, but the optimum antiviral doses and treatment duration, and the most favorable time to initiate therapy post-transplantation, have not been established. Dose reductions and treatment discontinuation rates are higher than desirable and likely limiting response rates. The need for safer and more effective antivirals in this special population of HCV-infected patients is obvious. Unfortunately, none of the new HCV investigational compounds in phase II or III studies in patients with chronic HCV infection (e.g. protease inhibitors, polymerase inhibitors, anti-apoptotic agents, RBV alternatives and others) are being evaluated in HCV-infected transplant patients. Given the great need for new therapies, clinical trials in transplant patients are to be strongly encouraged.

Several key questions regarding interferon-based therapies are of immediate importance to clinicians and should be the focus of future clinical trials. First, while the importance of growth factors in preventing treatment-induced cytopenias is unquestioned, whether growth factor use leads to higher SVR rates is unknown. Given the substantial cost of growth factors, determining their risk–benefit is a priority issue. Second, the controversy regarding interferon and rejection continues. Larger controlled studies are clearly needed to quantitate the risk of acute and chronic rejection accurately, and to identify the risk factors for rejection and best means of prevention. Finally, since SVR rates are less than 50% overall, determination of whether anti-HCV therapy offers other benefits, specifically a slowing of the rate of fibrosis progression in the absence of virologic clearance, is of major importance in this population.

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