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Management of Hepatitis C Infection after Liver Transplantation

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Contents

Abstract

Recurrent hepatitis C virus (HCV) infection after orthotopic liver transplantation (OLT) has been associated with progression to cirrhosis in ≈20% of patients, 5 years postoperatively. Accelerated decompensation has also been noted when compared with cirrhosis in non-transplant patients. Different treatment strategies are available for recurrent HCV infection post-OLT, but efforts are hindered by the modest response rates, poor tolerability and the risk of rejection as well as graft loss.

Anti-HCV immunoglobulin therapy to prevent graft infection with HCV has no established role at present but studies are ongoing. Treatment prior to transplantation in patients with decompensated cirrhosis has been evaluated but the results are too preliminary to make firm recommendations. Prophylactic interferon-based antiviral therapy in the early postoperative period to prevent graft infection was shown to have low response rates and high rates of adverse effects. Treatment of established recurrent HCV infection with combination peginterferon (pegylated interferon) and ribavirin is associated with 10–59% sustained virological response and the predictive value of a positive early virological response has been validated in the post-transplant setting. Improvement in inflammatory activity after viral eradication is well established, but fibrosis regression or stabilisation is less predictable and factors such as rejection and biliary complications may still

contribute to graft loss. Most studies have initiated therapy at least 6 months postoperatively in order to optimise patient tolerance and enable the addition of ribavirin. The use of adjuvant agents to treat drug-induced neutropenia and anaemia in this population is evolving and becoming a crucial part of therapy. Determination of optimal doses of both pegylated interferon and ribavirin, and guidance on when to stop treatment, as well as improving tolerability are important steps in achieving higher response rates and minimising drug toxicity.

Hepatitis C virus (HCV) infection-related end-stage liver disease is the leading indication for orthotopic liver transplantation (OLT).[1] Unfortunately, recurrent HCV infection post-OLT is universal and has been associated with decreased long-term graft and patient survival compared with other causes of liver disease.[2] Therefore, antiviral therapy for recurrent HCV infection has become a major issue facing transplant centres with a growing number of recipients developing HCV infection-related allograft fibrosis. Several studies have explored factors that could potentially contribute to the poor outcome of recurrent HCV infection. The degree of immunosuppression used to prevent rejection appears to be important. The use of corticosteroid boluses to treat rejection and the use of muromonab CD3 (OKT-3) as an induction agent, have been shown to be deleterious in the presence of recurrent HCV infection and most centres have abandoned these approaches. A better understanding is needed of the mechanisms leading to progressive disease in certain subgroups of recipients, and to differentiate them from the 30% of patients who continue to have stage 0 fibrosis after 5 years of follow-up post-OLT.[3]

The efficacy of antiviral therapy for recurrent HCV infection post-OLT is measured not only by viral eradication but also by allograft preservation. Secondary endpoints such as viral suppression, halting fibrosis progression, aminotransferase normalisation, and the adverse-effect profile of therapy are also of great importance in these patients. Three main approaches have been evaluated by several groups to manage recurrent HCV infection post-OLT. Antiviral therapy has been investigated in (i) patients with decompensated cirrhosis with HCV infection being considered for OLT; (ii) pre-emptively in the early post-OLT period before graft reinfection is well established; and (iii) in those with recurrent HCV infection with ongoing graft damage necessitating therapy in order to halt progressive fibrosis. This article summarises the current literature addressing issues related to different therapies of recurrent HCV infection both before and after OLT for HCV infection-related cirrhosis.

1. Natural History of Recurrent Hepatitis C Virus (HCV) Infection Post-Orthotopic Liver Transplantation (OLT)

As early as the first week postoperatively, the HCV RNA level increases ≈10- to 20-fold and plateaus at 1 month, infecting the allograft in virtually all patients, with higher levels noted in those with more severe recurrent hepatitis.[4-8] The clinical course and necro-inflammatory activity varies after transplant with 2–5% of patients developing severe cholestatic hepatitis, leading to early graft failure, and ≈20–25% showing progressive fibrosis leading to cirrhosis after 5 years.[7,9,10] On the other hand, approximately 30% of patients continue to have fibrosis stage 0 after 5 years of follow-up.[3] Studies have shown that high pre-transplant viral load, repeated intravenous corticosteroid boluses, older donor age, graft steatosis and heavier initial immunosuppression were associated with poor histological or graft outcome.[5,10-14] Furthermore, severe and early histological recurrence as well as severe biochemical abnormalities at the onset of hepatitis have been found to correlate with poor outcome.[10,15] The impact of HCV genotype on outcome remains unclear with some but not all studies demonstrating genotype 1 to be associated with worse outcome compared with non-1 genotype.[4] Finally, the post-

OLT level of viraemia has not been shown to be associated with genotype 1.[16]

1.1 Tacrolimus versus Ciclosporin-Based Immunosuppression

Although immunosuppression level appears to be a contributing factor for this course when compared with the course of HCV infection in non-transplant patients, no particular immunosuppressive regimen has been found to be superior in reducing the accelerated course of HCV progression post-OLT.[17] Although ciclosporin (cyclosporin) has been shown to have an *in vitro* suppressive effect on HCV replication, when a ciclosporin-based regimen was compared with a tacrolimus-based regimen, they both had comparable severity of recurrent HCV infection.[18] On the other hand, Firpi et al.[19] reported recently in a retrospective analysis of patients who received interferon-based antiviral therapy for recurrent HCV infection that patients who received ciclosporin-based immunosuppression achieved a higher sustained virological response (SVR) than those who received a tacrolimus-based regimen (46% vs 27%; p = 0.03). This study also showed that ciclosporin inhibited HCV replication *in vitro* and the combination of ciclosporin and interferon had additive effects on *in vitro* viral suppression. When compared with tacrolimus, ciclosporin was associated with a lower relapse rate in one study,[20] but both agents had comparable therapeutic outcomes in another trial.[21] Thus, while there may be modest antiviral effect of ciclosporin on HCV RNA levels, the use of ciclosporin has not consistently lead to improved outcomes with anti-viral therapy when compared with tacrolimus.

1.2 The Role of Corticosteroids in Recurrent HCV Infection

Several studies have evaluated the safety and the efficacy of a corticosteroid-free immunosuppression and its impact on recurrent HCV infection in the allograft.[22-28] These studies utilised different induction and maintenance immunosuppressive protocols, but all demonstrated that corticosteroid-free regimens were safely used and effective. One study found early metabolic complications including diabetes mellitus, hyperlipidaemia and hypertension to be significantly less frequent in the corticosteroid-free regimen.[25] Corticosteroid-free regimens had a comparable severity of recurrent HCV infection compared with regimens using corticosteroids in some studies,[23-25,27] while two studies showed a trend to lower severity of recurrent HCV infection.[22,26] Furthermore, the report by Margarit et al.[26] demonstrated a significantly lower rate of cirrhosis development at 3 years in the corticosteroid-free group that received tacrolimus only compared with the tacrolimus plus corticosteroid group (9% vs 45%; p = 0.04). Patient survival at 1, 3 and 5 years was 92%, 92% and 73%, respectively, for tacrolimus and 78%, 61% and 51%, respectively, for tacrolimus plus corticosteroid (p = 0.07). Other studies provided follow-up data for just 2 years, which may have contributed to the lack of survival advantage of corticosteroid-free regimens in patients with recurrent HCV infection.

1.3 Other Immunosuppressive Agents

Multiple corticosteroid boluses and the use of muromonab-CD3 to treat rejection have been associated with severe recurrent HCV infection and graft loss, respectively.[29] Induction therapy with anti-interleukin-2 antibodies did not demonstrate additional benefits in recipients with recurrent HCV infection and its role in liver transplantation is yet to be fully defined.[30-32] Conflicting data have been reported on the addition of mycophenolate mofetil (MMF), an inosine monophosphate dehydrogenase (IMPDH) inhibitor, to calcineurin inhibitors. No significant difference in HCV infection recurrence and outcomes was found in two randomised trials,[33,34] while MMF use was associated with increased risk of fibrosis progression in a third study that evaluated data from four transplant centres.[35] The Scientific Registry of Transplant Recipients database analysis showed that the addition of MMF to a tacrolimus-based regimen was associated with improved post-OLT 4-year survival in patients with and without HCV infection.[36] Thus, at this time, the preponderance of data suggests that the addition of

MMF to calcineurin inhibitor therapy is associated with outcomes not different from immunosuppressive regimens not including MMF.

The use of sirolimus in liver transplant recipients has been mainly limited to rescue therapy from calcineurin inhibitor-induced renal toxicity with no data to evaluate its role in recurrent HCV infection post-OLT, although this is currently under investigation.

1.4 HCV Infection After Live Donor Liver Transplantation

Preliminary data suggest that the histological progression of recurrent HCV infection in live donor liver transplantation (LDLT) appears to be comparable with HCV infection in recipients of deceased donors.[37,38] Earlier studies demonstrated a higher probability of severe HCV infection recurrence, the development of cirrhosis, the occurrence of cholestatic hepatitis and lower graft survival in LDLT,[39-41] although more recent studies have shown no significant differences between the two modalities.[42-44]

2. Liver Biopsy Interpretation in Subjects with Recurrent HCV Infection

Histological changes noted on liver biopsy due to recurrent HCV infection are variable. Approximately two-thirds of patients develop mild acute hepatitis manifested by the presence of prominent lobular inflammation, focal necrosis, acidophilic bodies and macrovesicular steatosis. This is usually followed by chronic hepatitis manifested by lymphoid aggregates in portal tracts, interlobular bile duct damage, macrovesicular steatosis and lobular infiltrates with apoptotic bodies.[45-48] Steatosis has been reported as a specific sign or even the sole manifestation of recurrent HCV infection in the allograft.[49,50] The role of liver biopsy in patients with recurrent HCV infection post-OLT to identify acute cellular rejection is hampered by the overlapping features such as chronic portal inflammation, ducal damage, apoptosis and even endothelialitis, which can be seen in both acute cellular rejection and recurrent HCV infection.[45,47,51-53] The histopathological differentiation of recurrent HCV infection from acute cellular rejection had relatively low interobserver and intraobserver agreement rates and showed low reliability; thus biopsies should typically be reviewed in a multidisciplinary approach.[54] Additional clinical tools are required to differentiate recurrent HCV infection from acute cellular rejection. Furthermore, clinical rather than histological parameters were found to more accurately predict outcome in recipients developing cholestasis thought to be due to either acute cellular rejection or cholestatic hepatitis HCV infection.[55] Criteria adopted by the International Liver Transplantation Society Expert Panel to define cholestatic hepatitis include the following:

1. abnormal liver chemistries >1 month post-OLT (usually <6 months);
2. hyperbilirubinaemia >6 mg/dL;
3. serum alkaline phosphatase and γ-glutanyl transferase >5 times the upper limits of normal;
4. characteristic histological state with ballooning changes in hepatocytes mainly in the perivenular zone, minimal inflammatory infiltration, bile duct proliferation without loss;
5. very high levels of HCV RNA;
6. absence of biliary complications or hepatic artery thrombosis.[56]

A liver biopsy performed 1-year post-OLT has been shown to help identify those with increased risk of developing progressive disease, thus allowing better targeting of antiviral therapy,[57] and this is now routinely performed in many transplant centres. Finally, annual liver biopsy is recommended in HCV-infected transplant recipients, given the high prevalence of abnormal histological findings and the progressive nature of the disease.[3] Measuring hepatic elastometry is being explored in the post-OLT setting and appears to be accurate in identifying those with advanced fibrosis.[58,59]

3. Management Options for Recurrent HCV Infection

Viral eradication is the ultimate goal of any strategy to prevent allograft failure as a result of recurrent HCV infection. While several studies have

questioned the overall benefits of antiviral therapy on fibrosis progression, when intention to treat analysis was performed, anti-viral therapy appeared to prevent histological progression of disease if viral eradication is successful.[60,61] Unfortunately, interferon-based therapy, with its lower tolerability in post-OLT patients, is the only available treatment modality that can eradicate the virus either temporarily or permanently. The use of maintenance therapy with low-dose interferon in those who cannot tolerate full-dose therapy or for whom such treatment failed has not been studied. Regardless of their timing in relation to transplant, studies of most interferon-based interventions have common features including low tolerability, limited eligibility and poor efficacy. This is further complicated by the increased risk of acute and chronic rejection as well as graft loss.[61-63]

In comparison with the significant benefits gained from oral antiviral agents and hepatitis B immunoglobulin (HBIg) for hepatitis B virus infection, there is an urgent need for agents that would enable us to provide a similar approach in the management of HCV infection perioperatively, but this has not been achieved so far. Utilising hepatitis C immunoglobulin (HCIg) in a fashion similar to HBIg has been evaluated recently in a randomised, open-label study and found to be well tolerated but serum HCV RNA levels were not suppressed in the treatment group.[64] Anti-HCV monoclonal antibodies have demonstrated neutralising activity against HCV viral particles *in vitro*, inhibited HCV infection of human liver fragments and have reduced the mean viral load in HCV-positive animals.[65] These antibody therapies may have the potential of preventing reinfection of the allograft after transplantation.

3.1 Prophylactic Antiviral Therapy Prior to OLT

There are six studies reporting experience with interferon-based therapy in pre-transplant patients aiming to prevent reinfection of the new graft.[66-71] A randomised pilot study using three interferon-α-2b regimens and ribavirin showed that five patients (33%) became HCV RNA negative with therapy and the two who were transplanted had re-emergence of HCV RNA postoperatively. This study was terminated because of 20 serious adverse effects encountered in 87% of enrolled patients, although this population had advanced cirrhosis with a mean Child-Pugh score of 11.9 ± 1.2.[66] The largest study included 124 patients with an average Child-Pugh-Turcotte (CPT) score of 7.4 ± 2.3 who received a low-accelerating-dose regimen. The initial dose of interferon-α-2b was 1.5MU three times a week, while ribavirin was initiated at 600 mg/day. Peginterferon-α-2b was given at half the standard dose during the retreatment of 15 patients (0.5 μg/kg/week). Incremental adjustments were made every 2 weeks to reach maximally tolerated or target doses. An SVR of 24% was achieved and 12 of 15 patients who were HCV RNA-negative before OLT remained HCV RNA-negative ≥6 months postoperatively. Twenty-two significant adverse effects were seen in 15 patients with two complications associated with mortality thought to be related to antiviral therapy.[67] Another study evaluated the efficacy of interferon-α-2b 3MU daily and ribavirin 800 mg/day in 30 patients awaiting liver transplantation. This study reported that of nine patients with undetectable HCV RNA who underwent OLT, six remained free of infection after a median follow-up of 46 weeks. Adverse effects were common and dose reduction was necessary in 63% of patients but no deaths were related to therapy.[68] This study showed that the positive and negative predictive values of ≥2 log decrease in HCV RNA at week 4 were 82% and 100%, respectively. Another study with a smaller number of enrolled patients showed that one-third of those who cleared HCV prior to OLT did not have evidence of disease recurrence post-OLT. This study used high-dose (5MU) interferon-α-2b daily.[70]

These studies suggest the possible applicability of this approach, although it should be limited to those with Child-Pugh class A or B cirrhosis, and there is still a significant risk of adverse events. Importantly, these studies did not include control groups and no definite conclusions can be made

about the association of therapy with an increased risk of serious infections, which are common in patients with decompensated cirrhosis. On the other hand, cirrhotic patients receiving interferon and ribavirin appear to be at increased risk of bone marrow suppression and worsening of the already marginal hepatic function while receiving antiviral therapy. Peginterferon has been shown to be more effective than regular interferon in non-cirrhotic patients with HCV infection, but there is limited experience on its use in those with decompensated cirrhosis.

In a study by Martinez-Bauer et al.,[69] 50 HCV-infected patients listed for OLT with expected time for transplant <6 months, were treated with peginterferon-α-2a and ribavirin until transplantation. This study reported a modest SVR of 28% with notable rates of adverse effects including anaemia (66%), neutropenia (20%), further decompensation (32%) and infections (32%). There were two deaths in this study and dose reductions were needed in 60% of patients. Predicting SVR in pre-transplant patients receiving interferon-based antiviral therapy was evaluated in two of the studies discussed in this section. One study found non-1 genotype, Child-Pugh class A (genotype 1 only), and ability to tolerate full dose and duration of treatment ($p < 0.0001$) were predictors of SVR.[67] Another study found pre-treatment viral load to be significantly lower in responders and a viral load decrease ≥2 $\log_{10}$ at week 4 of treatment to be the strongest predictor of virological response.[68]

On the basis of available data, prophylactic antiviral therapy in this setting to prevent recurrent HCV infection post-OLT has a limited role and may be associated with serious adverse events. Prophylactic antiviral therapy should not be considered in those with high model for end-stage liver disease (MELD) or CPT scores.

3.2 Pre-Emptive Antiviral Therapy

The pre-emptive antiviral therapy approach requires the institution of interferon therapy preferably before the expected peak in HCV RNA is reached and allograft infection with HCV is established, typically within the first 2–6 weeks postoperatively. Early studies evaluated interferon monotherapy with modest results, while later the addition of ribavirin provided some improvement in response rates.

Sheiner et al.[72] compared 41 patients who received no therapy with 30 patients who were given interferon-α-2b 3MU subcutaneously three times a week starting within 2 weeks after transplantation and continuing, if tolerated, for at least 1 year. This study reported a significant improvement in histological recurrent HCV infection rates at the end of therapy ($p = 0.017$). Another study by Singh et al.[73] reported in the same year randomised 24 patients to interferon-α-2b three times per week for 6 months or no therapy. Histological recurrence rates were comparable in both groups but recurrence was delayed in the interferon group. Both studies reported a high prevalence of adverse effects (30–50%). Mazzaferro et al.[74] reported better results when 36 patients received interferon-α-2b and ribavirin for 12 months achieving an SVR of 33%, while dose reduction was needed in 47% of the cohort. This study included 11 patients who were classified as Child-Pugh class A with a small hepatocellular carcinoma at the time of OLT, and six (50%) of the responders had genotype 2. It has been shown that transplant recipients with lower pre-OLT MELD or CPT scores are more likely to be eligible for therapy and be able to achieve full therapeutic doses of the antiviral medications.[75] Finally, a randomised, multicentre trial of interferon-α-2b and ribavirin versus placebo reported a lower SVR of 16% and significant anaemia developing in 57% of patients.[76]

Pre-emptive post-OLT therapy with peginterferon was associated with a modest response and a rate of unwanted adverse effects that is comparable with standard interferon, and more than the rate experienced in non-transplant patient with cirrhosis (table I). A large US-based multicentre study evaluating peginterferon-α-2a pre-emptive monotherapy reported significantly lower HCV RNA levels and favourable histological changes on biopsies in the treatment group,[77] which was associated with

Table I. The main trials using pre-emptive therapy in 4–6 weeks post-orthotopic liver transplantation for recurrent hepatitis C virus infection

Study	Antiviral regimen (no. of patients)	SVR (no. of patients [%])	Dose reduction (no. of patients [%])	Discontinue (no. of patients [%])
Sheiner et al.[72]	IFN (n = 30)	0	NA	10 [30]
	No therapy (n = 41)	0		NA
Singh et al.[73]	IFN (n = 12)	0	6 [50]	NA
	No therapy (n = 12)	0		
Mazzaferro et al.[74]	IFN + RBV (n = 36)	12 [33]	17 [47]	[0]
	No therapy (NA)	NA		
Reddy et al.[76]	IFN + RBV (n = 21)	[16]	10 [48]	NA
	Placebo (n = 11)	[0]		
Chalasani et al.[77]	PEG-IFN (n = 26)	2 [8]	11 [42]	8 [31]
	No therapy (n = 28)	[0]		9 [32]
Shergill et al.[75]	IFN or PEG-IFN (n = 22)	1 [4.5]	15 [68][a]	18 [41][b]
	IFN or PEG-IFN with RBV (n = 22)	4 [18]	19 [86][a]	

a Patients unable to tolerate 80% of treatment dose for 80% of study duration.

b Data for both groups.

IFN = interferon; **NA** = data not available; **PEG** = pegylated; **RBV** = ribavirin; **SVR** = sustained virological response.

an SVR of 8%. Patients with a neutrophil count <1500/μL, a platelet count of <75 000/μL and a haemoglobin count <10 g/dL were excluded from this study. This study used peginterferon-α-2a at a fixed dose of 180μg weekly in the treatment arm and the dose was reduced by 45μg when required per protocol because of adverse effects. Dose reduction was required in 42% of patients because of adverse effects (thrombocytopenia and/or neutropenia) and dropout rates were 31% and 32%, respectively, in the treatment and observation groups.

Another study randomised eligible recipients to interferon-α-2b (or peginterferon-α-2b when it became available) with or without ribavirin.[75] The interferon dose was 1.5MU daily for the first 2 weeks, then increased to 3MU daily for weeks 3–8, then dropped to 3MU three times a week or 1.5 g/kg for peginterferon with a tapering to stop in the last 4 weeks. The dose of ribavirin was increased gradually from a starting dose of 400 mg/day. This study showed an end-of-therapy and SVR of 13.6% and 9.1%, respectively. The combination therapy group had higher response rates but the difference was not statistically significant. Only 51 (41%) of 124 transplant recipients were eligible for therapy and 15% of patients were able to reach full-dose treatment. Dose reduction and discontinuation were required in 85% and 37% of subjects, respectively.

Finally, a recent retrospective report has demonstrated that pre-emptive therapy did not appear to slow fibrosis progression.[78]

On the basis of available data, no recommendations can be made about the use of pre-emptive antiviral therapy in the post-OLT setting. These studies indicate indirectly that this approach may be best avoided in those with high MELD scores prior to transplantation and those who have other comorbid conditions postoperatively that would predict a high rate of intolerance to interferon-based therapy.

3.3 Therapy of Established Recurrent HCV Infection

Therapy for established recurrent HCV infection in the allograft has been evaluated in at least 20 studies and many of them are reports on single-centre experience still in abstract form. Therapy was initiated in those with biochemically and histologically established recurrent disease, and in most reports, at least 6 months postoperatively (table II). This approach ensures recovery from surgery and sequela of cirrhosis, optimum renal function, and avoidance of therapy in patients who eventually have mild histological recurrence with normal or slightly elevated liver function tests. This approach has not been compared with the pre-emptive treatment nor has it been studied in large trials to evalu-

Table II. The main randomised trials reported on therapy for established recurrent hepatitis C virus infection post-orthotopic liver transplantation

Study	Antiviral regimen (no. of patients)	Responses (%)	Dose reduction (%)	Adverse effects (%)	Discontinuation of therapy or withdrawal (%)
Samuel et al.[82] a	IFNα-2b + RBV (n = 28) No therapy (n = 24)	SVR: 21 EVR: 32	NA	Anaemia: 25	43 29
Dumortier et al.[85]	PEG-IFN + RBV (n = 20)	SVR: 45	65	ACR: 25	20
Chalasani et al.[77]	PEG-IFN (n = 33) No therapy (n = 32)	SVR: 12	59		30 19
Ghalib et al.[86] a	PEG-IFNα-2b + RBV full dose (n = 32 pts) PEG-IFNα-2b + RBV low dose (n = 27)	SVR: 59 SVR: 18	NA	Death: 3	19 18
Picciotto et al.[87]	PEG-IFNα-2b + RBV (n = 61)	SVR: 28 EVR: 34	100		15
Duvoux et al.[81]	PEG-IFNα-2a + RBV (n = 101)	EVR: 61		ACR: 2	
Iacob et al.[88]	PEG-IFNα-2b + RBV (n = 35)	SVR: 22.8 NR: 42.8			
Martini et al.[89]	PEG-IFNα-2b + RBV (n = 86)	SVR: 33 naive SVR: 17 NR	93	ACR: 3 Neutropenia: 14	14
Morenoplanas et al.[80]	PEG-IFNα-2a + RBV (n = 30)	SVR: 46.7 EVR: 63	40	Infection/death: 6.7	36
Casanovas-Taltavull et al.[90]	PEG-IFN + RBV (36 pts)	SVR: 47	NA	NA	25
Berenguer et al.[21]	IFN (n = 31)/PEG-IFN (n = 36) + RBV	SVR: 33 EVR: 46	57	ACR: 3 (chronic 6)	40% with either drug
Petrolati et al.[79] a	PEG-IFNα-2a (n = 21) PEG-IFNα-2a + RBV (n = 21)	SVR: 33 EVR: 52 SVR: 33 EVR: 57	33 38	ACR: 14 ACR: 9	24 28
Neumann et al.[91]	PEG-IFNα-2b + RBV (n = 25)	SVR: 36 EVR: 68		Anaemia: 36 Neutropenia: 68	
Burra et al.[92]	IFN 6MU 3 × wk for 3mo + RBV 12mo (n = 55)	SVR: 20 EVR: 37	27	NA	27
Biselli et al.[93]	PEG-IFNα-2b + RBV (n = 20)	SVR: 45 EVR: 45			
Mukherjee[94]	PEG-IFNα-2a + RBV (n = 32)	SVR: 40.6			16
Bahra et al.[95]	PEG-IFNα-2a + RBV (n = 60)	SVR: 33 EVR: 46.6		Anaemia: 38 Neutropenia: 52	8
Lilly et al.[96]	IFN/PEG-IFN + RBV (n = 100)	SVR: 24 EVR: 49		ACR: 7	4

a Randomised.

ACR = acute cellular rejection; **EVR** = early viral response; **IFN** = interferon; **NA** = data not available; **NR** = nonresponders to prior therapy; **PEG** = pegylated; **RBV** = ribavirin; **SVR** = sustained virological response.

ate its efficacy. As seen with the pre-emptive approach, therapy has been associated with significant dose reductions and cessation of therapy. Patients with compensated cirrhosis of the allograft were excluded from two studies.[77,79] One study reported comparable SVR rates of 46% in those with or without allograft cirrhosis, but discontinuation of therapy was significantly higher in those with cirrhosis. This study had a small sample size of 30 patients and reported two deaths due to biliary sepsis while receiving therapy.[80] Biopsies performed at the end of therapy have consistently demonstrated improvement in histological grading indices in several studies,[81,82] but the difference lessened upon

further follow-up.[77,82] The lack of fibrosis stage improvement in these studies is probably related to short-term follow-up and small sample size with low SVR rates. Marked histological improvement has been demonstrated after a mean follow-up of 3 years in those who achieved SVR, although 20% developed worsening fibrosis despite viral clearance.[83,84]

Interferon monotherapy in earlier studies demonstrated modest histological improvement and initially raised concerns for induction of interferon-induced chronic rejection.[62] Several studies have reported on the experience of using combination therapy of interferon and ribavirin, and the majority of these studies were not randomised. The largest randomised trial included 28 patients in the treatment group who received interferon-α-2b 3MU three times a week subcutaneously and ribavirin (800–1200mg) daily (table II). It also included 24 patients in the observational control group.[82] SVR, which was the primary endpoint of this study, was achieved in 21% of the treatment group and end-of-therapy serum HCV RNA was undetectable in nine patients (32%). Sixteen patients were withdrawn from the study; 12 (43%) withdrawals were from the treated group and were due to anaemia (seven patients) and four (17%) from the control group. End-of-therapy biopsies demonstrated an increased proportion of patients with improvement in METAVIR activity scores[97] in the treatment group compared with the control (54% vs 21%). However, this difference was not significant on biopsies taken at the end of the follow-up period (25% vs 21%). All of the responders but one were treated for >4 years post-OLT and they all had stage 2 fibrosis or less. Of note, HCV RNA levels in the six patients who obtained SVR in this study were undetectable or had >2 log decrease at week 12 on therapy.

Peginterferon has been evaluated in several trials with or without ribavirin to treat established recurrent HCV post-OLT. Most studies were non-randomised, single centre experiences and showed slightly higher SVR compared with standard interferon, but the incidence of dose reductions due to adverse effects seemed to be comparable with both formulations, although no head-to-head comparison has been completed. In a randomised, controlled treatment versus no treatment trial of peginterferon-α-2a, only three patients (12%) achieved SVR.[77] Ten patients (30%) and six (19%) were withdrawn prematurely in the treatment and control groups, respectively. The incidence of acute rejection was higher but not statistically significant in the treatment group compared with the control group (12% vs 0%; $p = 0.1$).

Two randomised trials have reported preliminary results on the use of peginterferon and ribavirin combination therapy. In the first trial, 59 patients received peginterferon-α-2b 0.5 μg/kg/week and ribavirin 600 mg/day (dose increased to 800mg at week 4 if tolerated) for 4 weeks then, based on baseline randomisation, patients either continued with the same dose of peginterferon of 0.5 μg/kg/week or the dose was increased to 1.5 μg/kg/week for 48 weeks with a 24-week stopping rule if HCV RNA was still positive.[86] Fifty-nine percent of patients in the high-dose group achieved SVR compared with 18% in the low-dose group ($p < 0.001$). Fifteen percent of patients had to stop therapy due to adverse effects with two deaths reported in the high-dose arm.

In the second trial, 42 patients were randomised to peginterferon-α-2a 180 μg/week monotherapy (21 patients) or peginterferon-α-2a 180 μg/week plus a maximum tolerated dose of ribavirin (21 patients). Response rates were similar in both groups (33%).[79,98] However, three patients in the monotherapy group and one in the combination group withdrew because of acute rejection.

Several uncontrolled trials of peginterferon plus ribavirin combination therapy reported a significant variation in SVR from 22% to 59% as shown in table II. The main predictors of response were course completion and favourable genotype.[80,85,87-89] The rule of 80/80/80 (receiving 80% of the recommended doses of PEG-interferon and ribavirin for 80% of the recommended duration of therapy) that has been developed in non-transplant patients appears to be highly associated with the achievement of SVR in the setting of recurrent HCV infection post-OLT as well.[37,99]

Early virological response (EVR), defined by negative HCV RNA or a >2 log decrease in HCV RNA after 12 weeks of therapy, has been shown to be a good predictor of SVR in the post-OLT setting. In the trial by Dumortier et al.,[85] the 3-month viral response was a predictor of SVR as 10 of 11 responders had undetectable HCV RNA at 3 months, but none of the nonresponders cleared virus. This has been further demonstrated by others recently.[21,80,88,90] On the other hand, a 4-week >2 log decrease in HCV RNA was significantly associated with SVR in one study[88] and reported in 10 of 14 patients who achieved SVR in another study.[80] Considering the progressive nature of recurrent HCV and the risk of graft loss, the decision to discontinue therapy in those with who fail to achieve EVR should be individualised, particularly in those with advanced fibrosis or those who received subtherapeutic doses, until the negative predictive value of EVR has been established in a large cohort of liver transplant patients. For example, in the study by Berenguer et al.,[21] 1 of 18 patients who developed an SVR did not have an EVR, while the other two fully published studies reported that an EVR developed in all of those who achieved an SVR post-OLT.

4. Adverse Effects of Interferon-Based Antiviral Therapies

Myelosuppression as a result of interferon therapy was common in all trials discussed in this review, and therapy for anaemia and neutropenia with growth factors, where reported, was required in up to 50% of patients. Ribavirin induces dose-related haemolysis by accumulation of ribavirin triphosphate in erythrocytes.[100] Antiviral therapy may be initiated with a lower ribavirin dose (600 mg/day) and can be increased as tolerated. Anaemia can also be managed by erythropoietin analogues, iron store repletion, avoidance of bone marrow suppressive agents, and even blood transfusion. A novel approach by measuring ribavirin levels in post-OLT patients is being investigated, given that calcineurin inhibitor use is associated with up to a 25% reduction in glomerular filtration rate.[101] Neutropenia can be managed with granulocyte colony-stimulating factors and avoidance of other bone marrow suppressive agents. Other serious adverse effects including infections and death have also been reported in the trials evaluating antiviral therapy.

Acute and chronic rejection have been reported in several studies while patients were receiving interferon-based therapy. Acute cellular rejection can improve with cessation of antiviral therapy or it can lead to ductopenia and graft loss.[61,63] Furthermore, it has been shown that SVR is more common in those who develop acute cellular rejection.[21,79]

There are limited data on therapy of patients who develop cholestatic recurrent HCV infection.[102] Therapy has a low response rate and may be required indefinitely. Furthermore, the risk of rejection is high and retransplantation may be required while receiving therapy.[102] We have successfully treated two patients at our institution for cholestatic recurrent HCV infection with interferon and ribavirin with clearance of HCV RNA from the serum. Both patients developed signs of graft failure necessitating retransplantation and at surgery, intravenous interferon was administered during the anhepatic phase to prevent graft reinfection. Both patients are doing well with no evidence of recurrent disease at 36 and 24 months postoperatively, respectively.[103]

Finally, transplant patients with recurrent HCV have significantly decreased global quality of life, physical functioning scores and an increased incidence of depression.[104,105] Antiviral therapy may exaggerate depressive symptoms, but whether this can lead to dose reduction or withdrawal has not been fully evaluated in post-OLT setting. Antidepressant therapy was generally given in many of the trials mentioned in this reviews and it should be considered early on during antiviral therapy.

5. Retransplantation for HCV-Related Allograft Failure

Graft failure due to recurrent HCV infection is a growing problem facing transplant centres considering the low success rate in eradicating HCV infection. Liver retransplantation for all indications has

been associated with ≈25–30% reduction in 1- and 5-year survival compared with first transplantation.[106] Furthermore, some studies demonstrated lower survival in those who underwent retransplantation for recurrent HCV infection compared with retransplantation for all causes.[107,108] However, other studies have shown survival after retransplantation to depend mainly on predictors of poor outcome including donor age, bilirubin >10 mg/dL, serum creatinine >2 mg/dL, and shorter time since the first transplant operation.[109-112] This would require retransplantation to be performed when the patient has a low MELD score, which is not possible under current organ allocation policies. Retransplantation for recurrent HCV infection-related allograft failure remains a dilemma facing centres regularly, and the decision whether and when to transplant should be made on case by case basis.[113-115]

6. Conclusion

Recurrent HCV infection after transplantation is universal and the spectrum of allograft injury related to HCV infection recurrence in liver transplant recipients is highly variable ranging from mild histological abnormalities to allograft cirrhosis. The natural history of HCV infection recurrence is generally accelerated and, although patients may experience an initial mild recurrence of HCV infection, delayed severe liver damage is also possible. Treatment with peginterferon plus ribavirin is encouraging, but poor tolerability and modest response rates are major problems to be addressed. Repeat or protocol biopsies and potential antiviral therapy in patients with evidence of progressive fibrosis should be recommended in clinical practice, although proper histological criteria for treatment and optimal duration of therapy are still uncertain. Antiviral therapy and viral eradication may be still possible in a selected group of patients with end-stage liver disease at the pretransplant setting, but this approach is generally limited by the adverse effects of therapy.

Therapy of established recurrent HCV infection post-OLT is the most accepted method to manage recurrent HCV infection post-OLT. Liver transplant recipients are followed for recurrent disease and therapy is offered in those when protocol liver biopsy demonstrates a METAVIR fibrosis grade >1 with ongoing necroinflammatory activity. Initiating antiviral therapy earlier (at the acute HCV re-infection phase) has not provided additional benefit with regard to SVR and adverse-effect profile; as initially postulated compared with the non-transplant setting.[116] Considering that adherence to antiviral therapy is a major factor in a achieving an SVR, careful selection of patients for therapy as well as optimisation of renal function, immunosuppressive regimen (including corticosteroid withdrawal or avoidance if feasible), and planning for anaemia management are required prior to initiating therapy. Peginterferon may be initiated at full or reduced dose. Ribavirin is typically initiated at 600 mg/day and can be increased gradually to 1000 mg/day except in patients with genotype 2 or 3 where a dose of 800 mg/day is likely to be sufficient. Therapy is generally extended for 48 weeks except in patients with genotype 2 and 3 who achieve rapid viral clearance (4 weeks); who may be treated for 24 weeks.

Further improvements in outcome are likely to depend on the introduction of newer agents that can provide viral suppression or eradication with potentially fewer adverse effects. These future therapies may include protease inhibitors, polymerase inhibitors, ribavirin analogues and other immune modulators that are currently undergoing evaluation in non-transplant patients.

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