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TOPIC HIGHLIGHT

Angelo Zullo, MD, *Series Editor*

Prevention of hepatitis C recurrence after liver transplantation: An update

Marco Carbone, Ilaria Lenci, Leonardo Baiocchi

Marco Carbone, Liver Unit, Queen Elizabeth Hospital, Birmingham, B15 2TH, United Kingdom
Marco Carbone, Ilaria Lenci, Leonardo Baiocchi, Hepatology Unit, Department of Internal Medicine, University of "Tor Vergata", 00133 Rome, Italy
Author contributions: All the authors contributed to the writing of this manuscript.
Correspondence to: Leonardo Baiocchi, MD, PhD, Assistant Professor, Hepatology Unit, Department of Internal Medicine, University of Rome "Tor Vergata", Via Montpellier 1, 00133 Rome, Italy. baiocchi@uniroma2.it
Telephone: +39-6-72596875 Fax: +39-6-72596875
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Abstract

Hepatitis C related liver failure and hepatocarcinoma are the most common indications for liver transplantation in Western countries. Recurrent hepatitis C infection of the allograft is universal and immediate following liver transplantation, being associated with accelerated progression to cirrhosis, graft loss and death. Graft and patient survival is reduced in liver transplant recipients with recurrent Hepatitis C virus (HCV) infection compared to HCV-negative recipients. Many variables may impact on recurrent HCV liver disease. Overall, excess immunosuppression is believed to be a key factor; however, no immunosuppressive regimen has been identified to be more beneficial or less harmful. Donor age limitations, exclusion of moderately to severely steatotic livers and minimization of ischemic times could be a potential strategy to minimize the severity of HCV disease in transplanted subjects. After transplantation, antiviral therapy based on pegylated IFN alpha with or without ribavirin is associated with far less results than that reported for immunocompetent HCV-infected patients. New findings in the field of immunotherapy and genomic medicine applied to this context are promising.

Key words: Hepatitis C; Liver transplantation; Recurrence; Immunosuppression; Treatment

Peer reviewer: Dr. Alessandro Grasso, Chief, Internal Medicine and Gastroenterology Unit, San Paolo Hospital, Savona, Italy

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INTRODUCTION

Chronic hepatitis C is the most common indication for liver transplantation (LT) in Western countries[1]. It is recognized that recurrence of hepatitis C virus (HCV) infection after LT is immediate and universal, based on the presence of HCV-RNA in serum and liver. However, the recurrence of HCV disease requires protocol and/or clinically indicated liver biopsies that report both grade and stage of disease.

Despite early reports suggesting that recurrent HCV infection after LT was a relatively benign condition[2-4], numerous later studies have shown that histological progression of HCV liver disease is accelerated following LT[5]. As a result, 30% of liver transplanted patients with HCV develop graft cirrhosis within 5 years[6]. This rapidly progressing disease ultimately determines reduced graft and patient survival[1,6-8]. At 5 and 10 years after LT, survival is 75% and 68% respectively, compared with 85% and 78% for other indications[1,7,8]. Forman and co-authors, in the analysis of the United Network for Organ

Sharing (UNOS) database of patients grafted between 1992 and 1998, showed that transplantation in HCV-positive recipients was associated with an increased death rate of 1.23 (95% confidence interval: 1.12-1.35) compared with transplantation in recipients without HCV[1].

A more recent analysis of the UNOS database by Futagawa *et al*[9] evaluating outcomes during two successive periods (1992-1996 and 1997-2002) among patients transplanted for different etiologies, found a lack of improvement in long-term survival; and this was attributed to the poor survival of HCV recipients (5 year graft survival of 65%), HCV-related cirrhosis being the leading indication for liver transplant in the US. Also, the incidence of recurrent HCV was higher in the more recent years (1997-2002) compared to the previous period, although not statistically significant. The reason for this was unknown.

With the clear understanding that HCV infection of the graft impairs both graft and patient survival, there has been intensive investigation focusing on variables associated with poor outcome, in the attempt to improve the results of LT in HCV patients.

In this article, we review the factors that may impact on recurrent HCV after LT and the current strategies to minimize the severity of recurrence and ameliorate its course.

IMMUNOSUPPRESSION

Immunosuppression is believed to be the principal factor in determining the severity of recurrent HCV liver disease, and thus, the poorer outcome of HCV patients after LT, in comparison with HCV immunocompetent subjects in the general population.

However, there is no consensus about the agent or regimen responsible for the severity of evolution of HCV recurrence. The First International Liver Transplantation Society Consensus Conference in 2003 stated that the optimal strategy is to achieve a balance between prevention of acute and chronic rejection while minimizing the potential negative effects of immunosuppression on recurrent hepatitis C[10].

Data available on the effect of the different immunosuppressive agents on HCV replication and/or progression of recurrent hepatitis C are limited by many factors, such as: (1) the retrospective nature of the studies; (2) the lack of HCV-RNA data and of routine protocol liver biopsies in the majority of the reports; and (3) the heterogeneity of immunosuppressive regimens. All these aspects prevent a clear determination of the specific effect of each individual drug on HCV disease recurrence.

Steroids

Steroids, including both the total steroid dose and, most markedly, steroid bolus treatment for rejection, have historically been associated with worse HCV outcomes[11,12]. Therefore, since the second half of the nineties, many transplant centers have adopted a steroid-free regimen or rapid steroid tapers, reporting favorable results[13-16].

However, later studies have demonstrated a worsening of hepatitis C outcomes after LT during the era in which steroid and immunosuppressive minimization strategies were employed, even if the results of the studies may have been influenced by other changes occurring in the LT setting, such as increased donor age[5].

Recent data regarding the use of steroids for immunosuppression in HCV positive LT patients are controversial.

Klintmalm and co-authors, in a large (n = 312) randomized controlled study, did not find any differences in terms of recurrence of HCV and patient or graft survival in immunosuppressed subjects with or without steroid treatment after LT[17].

A meta-analysis of 19 randomized controlled trials (RCTs) on steroid avoidance after LT, conducted in 2008 by Segev and co-authors, evidenced that HCV recurrence was lower in patients not assuming steroids (RR = 0.90, P = 0.03). The results of this study are, however, limited by the heterogeneity of trials, the relatively small size of many RCTs and the short-term follow-up[18].

Also in regard to steroid use, some authors have suggested that rapid changes in the patients' immunological status may lead to worse hepatitis C outcome, possibly by enhancing viral replication during the period of intense immunosuppression, with a destruction of HCV infected hepatocytes during the phase of immune reconstitution[19]. Three studies, two retrospective and one prospective, supported this hypothesis, reporting improved outcome of recurrent hepatitis C when a slower steroid taper was adopted. However, in the prospective study, no differences were found in overall survival or death from recurrent hepatitis C[20-22]. In LT practice, both steroid boluses for mild episodes of acute rejection as well as their very rapid tapering are likely to be deleterious strategies in HCV patients and it seems wise to avoid these approaches.

Calcineurin-inhibitor

With regard to the impact of Calcineurin-inhibitor (CNI), many studies, mostly retrospective, have not found relevant differences between cyclosporine (CyA) and tacrolimus (Tac)-based immunosuppressive regimens in terms of HCV recurrent disease or survival[7,23-31].

The prospective studies comparing Tac to CyA have evaluated, in large part, other end-points, such as rejection rate and/or short-term survival, without addressing the problem of HCV recurrence[32-34].

In a prospective randomized controlled study of 495 recipients with HCV infection, no difference was detected in the histological recurrence rate of hepatitis C between patients receiving CyA or Tac in the first year after LT[35].

In 2006, Berenguer and co-authors conducted a meta-analysis of 5 RCTs, comparing Tac and CyA after LT and with a minimum follow-up of 12 mo. The analysis, including a total of 366 transplant recipients, showed that

Table 1 Outcome of hepatitis C virus liver transplanted patients treated with cyclosporine or tacrolimus-based immunosuppression in studies including protocol liver biopsie

Ref.	Time of biopsy (yr)	CyA-based regimen		Tac-based regimen		*P* value
Gane *et al*[142]	At 1 and 5[1]	No hepatitis	12/109	No hepatitis	3/21	0.1
		Mild chronic hepatitis	59/109	Mild chronic hepatitis	11/21	
		Moderate chronic hepatitis	30/109	Moderate chronic hepatitis	5/21	
		Cirrhosis	8/109	Cirrhosis	2/21	
Testa *et al*[143]	1	Evidence of recurrence	72/156	Evidence of recurrence	10/18	0.4
Berenguer *et al*[144]	1	F0	16/44	F0	17/46	NS
		F1	16/44	F1	15/46	
		F3	8/44	F3	9/46	
		F4	4/44	F4	5/46	
Berenguer *et al*[37]	1	F = 3-4	27/90	F = 2-3	22/91	0.37
	≈ 2	F = 3-4	42/110	F = 3-4	36/97	0.8

[1]It is not clearly specified in the paper when liver biopsies have been performed. CyA: Cyclosporine; Tac: Tacrolimus; NS: Not significant.

patient and graft survivals were similar. Unfortunately, histological and viral data were limited[36].

The same author recently published a large prospective study, showing that the choice of CNI does not influence the histological severity of recurrent HCV. In fact, advanced fibrosis (bridging fibrosis and cirrhosis) was detected in the first year biopsy in nearly 30% of patients in disregard to the use of either CyA or Tac and no differences in survival at 1 year and 7 years were observed[37] (Table 1).

There is some emerging "*in vitro*" evidence that CyA may exert an antiviral effect on HCV, requiring concomitant administration of interferon; this may be explained by the inhibition of the binding of NS5B to cyclophilin B, a functional regulator of the NS5B-RNA-dependent RNA polymerase[38].

While at present there are no elements to prefer either CyA or Tac in HCV patients, some authors propose a two step immunosuppression in which Tac could be used as initial treatment, better preventing cellular rejection, for its greater immunosuppressive potency. A possible switch to CyA may be adopted later during interferon-based antiviral therapy, taking advantage of cyclophilin-inhibiting properties of this latter drug[39].

Antimetabolites

The impact of the antimetabolites on HCV recurrence after LT remains an open issue.

Many studies have shown an antiviral and antifibrotic effect of mycophenolate mofetil (MMF)[40-44]. Faola *et al*[45] reported decreased 3 month HCV-RNA levels after induction with MMF in HCV positive liver transplant recipients.

In 2005, Bahra *et al*[46] evidenced that patients treated with MMF and CNI taper presented a significantly decelerated impairment of liver graft histology compared to a matched control group on CNI only, without any difference in terms of viral load. Similar findings have recently been reported by our group on a small population of HCV positive recipients switched from CNI to MMF compared with a control group of recipients remaining on CNI. The CNI group presented a significant increase of fibrosis with a yearly fibrosis progression rate of 0.33 ± 0.24 *vs* 0.05 ± 0.44 in the MMF group ($P = 0.04$)[46].

These data are in contrast with a previous report showing a significant impairment of liver histology after MMF treatment without tapering of CNIs[47].

MMF can be beneficial for liver inflammation and fibrosis because it allows CNI reduction and therefore a reduction of immunosuppression, without increasing the risk of acute rejection; however, a direct effect, mediated by the inhibition of lymphocyte proliferation through the block of the guanine nucleotides necessary for DNA synthesis, along with an antiviral effect, may also explain the decreased inflammatory activity and, therefore, the beneficial impact on fibrosis progression.

Furthermore, MMF, added to Tac and steroids, has been associated with an improved survival in patients with HCV compared to those treated with Tac and steroids alone, as shown in 2005 by the analysis of the Scientific Registry of Transplant Recipients database[48].

Regarding azathioprine, its impact on HCV recurrent disease has been recently evidenced by Manousou and co-authors who analyzed 103 recipients, randomized to Tac monotherapy ($n = 54$) or triple therapy with Tac, azathioprine and steroids ($n = 49$); those on triple therapy had a slower onset of histologically proven severe fibrosis and portal hypertension in comparison with those on monotherapy. The beneficial effect of the triple therapy in this study may be attributed to the long-term azathioprine therapy, as suggested by the authors[49].

Two large randomized trials comparing MMF to azathioprine in a maintenance immunosuppressive regimen showed no significant differences in either rates of recurrence of hepatitis C or outcomes in HCV infected patients in the study *vs* controls[47].

Other immunosuppressants

T-cell depleting therapies, such as Alemtuzumab (Campath) are very effective in the treatment of refractory acute rejection, although caution should be used in patients who are HCV positive[50,51]. Interleukin-2 receptor antibody-based therapy does not seem to be associated with a deleterious effect on HCV recurrence[52].

Complete weaning of immunosuppression

Some authors speculated that progression of HCV disease may be more related to excessive administration of immunosuppressant post LT, rather than the long-term effect of a specific immunosuppressive agent[37].

With this perspective, in our center we attempted the complete withdrawal of immunosuppression in thirty HCV recipients. Complete weaning was feasible only in eight (25%) patients. These subjects, however, exhibited a slower rate of fibrosis progression, a lower necro-inflammatory score, improved liver tests and lower HCV-RNA levels compared to those who did not achieve sustained immunosuppression withdrawal[53]. While 6.5 years follow-up data showed a less marked impact of the immunosuppression free state on the progression of HCV disease, a reduction of IS-related morbidity and an increase of the quality of life was recorded[54].

EXTENDED CRITERIA DONORS

The rising demand for LT along with the shortage of organs is a critical issue in the liver transplant field. In order to expand the donor pool, livers from extended criteria donors (ECD), including older donors, fatty livers, longer ischemia time and donation after cardiac death (DCD), have been increasingly utilized. Grafts of reduced quality from ECD may show an increased sensitivity toward additional damaging events such as ischemia/reperfusion injury, acute rejection episodes or recurrent hepatitis C.

Donor age

Donor age is an established risk factor for severity of HCV recurrence and reduced graft and patient survival[7,55,56]. In 2005, the analysis of the US Scientific Registry of Transplant Recipients, including 3463 patients with hepatitis C, evidenced that donor age between 41 years and 50 years was associated with a 67% increase in the risk of graft loss; the risk increased to 86% for donors between 51 years and 60 years of age and was more than 2-fold greater when donors were older than 60 years[57]. Interestingly, Selzner *et al*[58] showed that younger HCV positive patients with older grafts had better long-term results when compared with older HCV positive recipients receiving older grafts. Ideally, HCV-infected transplant recipients should not receive organs from older donors; however, considering the vast number of HCV-infected patients awaiting LT, this may not be feasible for many programs.

Steatosis

Steatosis has been shown to accelerate the progression of HCV disease in immuno-competent patients; moreover, a strong association exists between the presence of donor steatosis and the development of primary nonfunction after LT[59]. Literature regarding the potential impact of steatosis on post-LT outcome in HCV recipients is scarce and no standard grading of steatosis is used; thus, no comparison is possible. Two recent studies have addressed this question and found that steatotic grafts do not have a negative impact on the progression of HCV recurrence and on patient survival in HCV positive recipients[60,61]. Different results were reported by Briceño and coworkers who evidenced that HCV recurrence was earlier and more frequent in recipients with moderate-severe steatosis. Therefore, the authors suggest that grafts with a steatosis > 30% should be avoided in HCV positive recipients[62]. Considering the conflicting results, no recommendation can be drawn in this context.

Ischemia time

Prolonged cold and warm ischemia times have also been identified as risk factors for more severe post-LT HCV infection[63].

Donors after cardiac death

The use of livers from DCD is a recovery technique based on cardiopulmonary rather than neurological criteria for death, and the warm ischemic time is typically prolonged. It is associated with a significantly higher risk of graft failure and development of biliary complications[64-67], although more recent studies have reported good clinical outcomes[68,69].

Two recent studies evaluated the impact of DCD livers on survival in HCV positive recipients. Yagci and coworkers evidenced a reduced 1 year and 5 year graft survival in the DCD group compared to the donation after brain death group (55% and 46% versus 85% and 78%, respectively; $P < 0.0003$)[70]; Tao and coworkers showed a reduced 1 and 5 year graft survival in the DCD group, although the difference is not significant (70% and 61% *vs* 82% and 74%, respectively, $P = 0.24$). However, the rates of severe HCV recurrence (re-transplantation or death due to recurrent hepatitis C and/or the development of stage 4/6 fibrosis or more within 2 years) were similar in the two groups[71].

The evidence is not sufficiently complete to advise against the use of DCD liver in this setting; additional studies with a large number of patients are required to fully determine how HCV positive patients can truly benefit from the use of DCD livers. According to experts, a donor graft biopsy is highly recommended when a DCD liver is used in an HCV positive recipient[72].

LIVING DONOR LIVER TRANSPLANTATION

Living donor LT (LDLT) is a further important strategy to increase the pool of organs available for patients awaiting LT. There are several theoretical advantages over deceased donor LT (DDLT), including reduced cold ischemia time, generally younger donor age, lack of steatosis and the ability to perform the transplant electively. Theoretically, these factors may positively affect graft outcome. However, controversy remains as to whether HCV recurs

with greater severity in LDLT and whether this negatively affects graft and patient survival.

Early reports suggested that HCV infection recurred with greater severity in recipients of LDLT compared with recipients of DDLT[73-75].

A more severe HCV recurrence in LDLT could be explained by: (1) human leukocyte antigen homology between donor and recipient[76]; (2) HCV replication in proliferating hepatocytes; (3) a greater relative immunosuppression[77] in particular; and (4) more biliary and vascular complications, thus enhancing fibrosis progression[78].

In 2007, the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL), involving different liver transplant centers in the USA and including 275 HCV patients, showed that graft survival rates for LDLT and DDLT were similar, once centers have sufficient experience with LDLT[79]. Moreover, the authors found no differences in terms of histological features or time to progression to Ishak stage 3 or more, at 1 year after transplant between the two groups. However, only 28% of the HCV positive population in this study received a liver biopsy at 1 year after transplantation. These findings were confirmed in other studies[80-82].

In 2008, Selzner and coauthors evidenced a slower fibrosis progression in LDLT recipients than in DDLT recipients (DDLT: 0.19 fibrosis stage/year *vs* LDLT: 0.11 fibrosis stage/year; $P < 0.05$), showing for the first time a possible beneficial impact of LDLT on HCV recurrence; the authors explained that this finding was likely due to younger donor age in LDLT recipients[83].

A strategy to improve the outcome of LDLT in HCV positive disease would be to treat HCV infection before LT, planning the optimal timing to initiate antiviral therapy; this is easier compared to DDLT since LDLT is a scheduled surgical procedure.

It is well known that the incidence of biliary complications (or vascular complications leading to biliary leaks or stenosis) can be reduced in experienced hands after the learning curve[84].

Some authors also suggest that an LDLT program should be preferentially started in individuals with alcoholic cirrhosis, cholestatic diseases or hepatitis B virus-related cirrhosis, in whom the graft will not unequivocally suffer cumulative injuries[85]. This latter point, however, has not been validated.

CYTOMEGALOVIRUS INFECTION

Cytomegalovirus (CMV) infection has been associated with an increased risk for severity of HCV recurrence. It is not clear whether this is correlated to the inherent immunosuppressive properties of the CMV itself or if CMV infection is only a surrogate marker for over-immunosuppression[10]. While CMV prophylaxis is largely used when needed in the transplant protocols, its impact on HCV recurrence is difficult to assess.

TREATMENT

Current approaches to the management of HCV recurrence after LT are represented by pre-transplant antiviral therapy, with the goal of preventing re-infection of the graft and post-transplant antiviral therapy, with the goal of eradicating recurrent infection, thus preventing recurrent disease and graft loss.

Hepatitis C therapy before LT

The primary goal of pre-transplant antiviral therapy is the achievement of an undetectable HCV RNA level prior to transplantation eliminating the risk of re-infection of the graft[86].

Antiviral treatment with a standard regimen of Pegylated-Interferon (Peg-IFN) and Ribavirin (RBV) for patients with compensated cirrhosis (Child Pugh Class A) is widely accepted and recommended by international practice guidelines[87,88]. On the other hand, antiviral treatment of patients with decompensated cirrhosis (Child class B or C) represents a far more problematic approach.

Everson and co-workers analyzed the largest cohort ($n = 124$) of HCV-candidates for LT (mean CPT score = 7.4; mean MELD score = 11) undergoing antiviral treatment with interferon (peginterferon and nonpegylated forms) and RBV with a low-accelerating dose regimen, reporting an on-treatment virological response rate of 46% and a SVR rate of 24% (50% in genotype 2 or 3 and 13% in genotype 1). Seventy-one percent failed to achieve full doses and 13% discontinued early. Recurrent HCV infection was prevented in all patients achieving SVR[86]. Similar rates were reported in another experience with a smaller population[89].

The achievement of "on-treatment virological response" represents a secondary goal in pre-transplant treatment, as it has been shown to significantly reduce the risk of graft reinfection[90]. Forns and co-workers treated 30 patients (50% Child-Pugh class A), starting the treatment when the expected time to LT was around 4 mo; the rationale was that most virological responders achieve HCV-RNA undetectability by week 12 and this could be sufficient to prevent infection after removing the main source of virus. 9 (30%) of 30 patients achieved on-treatment virological response, which persisted in 6 (20%) after transplantation.

Pre-transplant treatment should be limited to patients with mild liver decompensation as those with advanced decompensation (Child-Class B to C or MELD >18) have a high risk for severe complications[10,91].

Close monitoring during treatment is suggested and the therapy should be administered in liver clinics affiliated with liver transplant programs. In order to manage severe cases of liver decompensation, patients should ideally already be on the list for transplantation before initiation of antiviral therapy[87].

Good candidates for pre-transplant therapy would be naïve patients or prior relapsers of standard IFN and RBV treatment, as the chances for an on-treatment virological response before transplant are relevant in these groups. Furthermore, good candidates may be patients with living donors, with a predictable timing of transplantation, patients with compensated cirrhosis and those

Table 2 Results of studies on treatment with Pegylated interferon and Ribavirin of recurrent hepatitis C after liver transplant

Ref.	Yr	Type of Study	Time since LT (mo)	*n*	Genotype (%)	Antiviral Therapy	SVR (%)	Discontinuation (%)
Rodriguez-Luna *et al*[88]	2004	Prospective, uncontrolled	4.2	19	63	Peg-IFN 0.5-1.5 μg/kg/wk + RBV 400-1000 mg daily x 48 wk after neg. RNA	26	49
Neff *et al*[89]	2004	Retrospective, uncontrolled	23.5	57	98	Peg-IFN 1.5 μg/kg/wk + RBV 400-600 mg daily x 48 wk	14	32
Dumortier *et al*[97]	2004	Prospective, uncontrolled	28	20	80	Peg-IFN 0.5-1.0 μg/kg/wk + RBV 400-1200 mg daily x 48 wk	45	20
Castells *et al*[107]	2005	Prospective, controlled	3.8	24	100	Peg-IFN 1.5 μg/kg/wk + RBV 400-800 mg daily x 48 wk	35	13
Berenguer *et al*[102]	2006	Retrospective, uncontrolled	16.6	36	89	IFN and RBV/Peg-IFN and RBV	18	40
Oton *et al*[103]	2006	Prospective, uncontrolled	63.3	55	91	Peg-IFN 180 μg/1.5 μg/kg/wk + RBV 11 mg/kg/d x 48 wk	24	7
Mukherjee *et al*[104]	2006	Retrospective, uncontrolled	16	32	75	Peg-IFN 180 μg + RBV 1000-1200 mg daily x 48 wk	34	15
Mukherjee *et al*[104]	2006	Prospective, uncontrolled	20	39	79	Peg-IFN 1.5 μg/kg/wk + RBV 800 mg daily x 6-12 mo	33	43
Fernandez *et al*[105]	2006	Prospective, uncontrolled	32	47	93	Peg-IFN 1.5 μg/kg/wk + RBV 800-1000 mg daily x 48 wk	23	21
Neumann *et al*[106]	2006	Prospective, uncontrolled	38	25	80	Peg-IFN 1.0 μg/kg/wk + RBV 600 mg daily x 48 wk	36	4
Picciotto *et al*[94]	2007	Prospective, uncontrolled	25	61	87	Peg-IFN 1 μg/kg/wk RBV 600-800 mg daily x 6-12 mo	28	15
Angelico *et al*[108]	2007	Prospective, controlled	48	21	81	Peg-IFN 180 μg + RBV 200-800 mg daily x 48 wk	33	55
Carriòn *et al*[140]	2007	Prospective, controlled	14.5	54	92	Peg-IFN 1.5 μg/kg/wk + 400-1200 mg daily x 48 wk	33	39
Sharma *et al*[141]	2007	Retrospective, uncontrolled	16	35	77	Peg-IFN 90-180 μg/0.5-1.5 μg/kg/wk + RBV 800 mg daily x 48 wk	37	74
Zimmermann *et al*[107]	2007	Prospective, uncontrolled	9.4	26	88	90 μg/wk for 4 wk then 135-180 μg/wk + 600 mg for 5 wk, then 800–1200 mg x 48 wk	19	11

LT: Liver transplant; IFN: Interferon; Peg: Pegylated; RBV: Ribavirin; SVR: Sustained virological response.

with hepatocellular carcinoma, who typically have lower MELD scores.

Recent data suggest that thrombopoietin receptor agonists, such as eltrombopag, may be a useful tool for improving pretreatment platelet counts in HCV cirrhotic patients who would otherwise be ineligible for therapy[92].

Treatment of established hepatitis C recurrence

The most widely used strategy involves initiating antiviral therapy once the consequences of the recurrence of HCV infection are detected on liver biopsy. The goal of therapy is to achieve viral eradication and this is associated with a survival benefit[93-95].

Treatment duration after transplantation is generally 12 mo, regardless of HCV genotype. The SVR rate is far less than that reported for immunocompetent HCV-infected patients. The mean overall SVR rate in the studies considering the efficacy of Pegylated-IFN and RBV was 30.2%, with a range of 8%-50%, 28.7% for genotype 1, with a range of 12.5%-40% and 71%-100% in patients with genotype 2 (Table 2). Secondary end-points of the treatment to be considered are the biochemical response (around 60% of cases) and histological improvement, in terms of reduction of inflammation, although this seems to be confined only to patients achieving a SVR.

Tolerance is worse compared with nontransplant patients with chronic hepatitis, with a percentage rate of dose reduction and discontinuation of 68 and 25, respectively. Usually, RBV is initiated at a dose of 400-600 mg daily and then increased slowly according to patient tolerability. The use of growth factors is common due to the high prevalence of hematological side effects[94,96-108].

The same SVR on treatment predictor used in the non-transplant setting, such as early virological response (EVR), treatment adherence, baseline viremia and HCV genotype, seem to also be reliable after LT.

Recently, Berenguer *et al*[50], in a retrospective analysis of 107 recipients treated with Peg-IFN and RBV, evidenced a strong relationship between donor age and outcome of antiviral therapy, as treatment failure was significantly more frequent in recipients of grafts from older donors. Authors recommend that antiviral therapy should be started in the early stages of disease in recipients of grafts from old donors, in whom the risk of progressive recurrent disease is higher and the chances of antiviral success are lower.

IFN-therapy after transplant is historically associated with a potential risk of acute cellular rejection (ACR), due to the immunomodulatory properties of IFN. The reported incidence of ACR ranges from 0 to 25%, with a mean incidence of 12%. The frequency and severity of ACR is typically not greater than that reported in patients

with recurrence of HCV infection who are not receiving antiviral therapy[109].

A higher risk of developing alloimmune hepatitis is reported, typically after HCV RNA clearance (approximately 5% of cases)[110].

Preemptive antiviral therapy and early therapy

In the preemptive strategy, the treatment is started within the first few weeks post-transplantation, when HCV-RNA values are low, before peaking at 3 mo to 4 mo post-transplantation. Candidates for preemptive therapy are patients without significant post-transplant complications, such as cytopenias, renal dysfunction and infections.

There are only two RCTs reporting the safety and efficacy of peginterferon alfa-2a in the early postoperative period[110] but the sample size is small. In the "prophylaxis trial", the treatment was initiated within 3 wk after LT and achieved a SVR of 8% (n = 2). In the "treatment trial", where the treatment was started 6 mo post-LT, the SVR was 12% (n = 5). The rate of discontinuation of therapy was 31%.

Non-randomized preemptive trials reported rates of SVR ranging from 5% to 33% in genotype 1 patients and from 14% to 100% in genotype 2/3 patients. The reported rate of treatment discontinuation ranged from 0% to 57% and dose reductions (ranging from 28% to 85%) were required more frequently for RBV rather than for interferon[111-114].

Interestingly, Kuo *et al*[115], analyzing a cohort of recipients receiving preemptive therapy, evidenced a long-term histological benefit in those receiving preemptive therapy, even if non-responders; fibrosis score $\geqslant$ 2 at 48 mo post-LT was reported in 22% patients undergoing preemptive therapy versus 49% of those that did not receive preemptive therapy (P = 0.08).

Another strategy consists of starting the antiviral therapy at the first clinical manifestation of "acute" recurrent HCV, usually occurring within the first 6 mo after transplantation ("early therapy"). SVR rates range from 13% to 35% in genotypes 1 and the tolerability seems to be improved (discontinuation 0%-13%). However, early preemptive therapy is not suitable for all transplant recipients[107,116,117].

Considering its low tolerability profile and the dismal results in terms of SVR, preemptive and early antiviral therapies are not largely recommended for the treatment of HCV recurrence, except in patients at high risk for progressive disease.

Adoptive immunotherapy

The immunosuppressive regimen currently used after LT reduces the adaptive immune components but effectively maintains the innate components of cellular immunity[118-120]. The enhancement of the natural killer cellular response that plays a pivotal role in innate immunity may be a promising immunotherapeutic approach, also in the prevention of HCV recurrence post-LT[121].

Ohira *et al*[122] report an interesting immunotherapeutic approach for preventing post-transplant HCV recurrence, based on adoptive transfer of interleukin 2 (IL-2)/anti-CD3 monoclonal antibody (OKT3)-treated liver allograft-derived lymphocyte pools enriched in natural killer and natural killer T cells.

This was a phase 1 clinical trial in which 14 patients were treated with liver allograft-derived lymphocytes. During the first months after LT, HCV RNA levels were significantly lower on average in the treated recipients than in the controls. HCV RNA became undetectable after immunotherapy in two treated patients 4 wk after LT but in none of the controls. In one of the treated patients, HCV RNA was still undetectable 20 mo after LT, whereas HCV infection recurred 2 mo after transplantation in the second one.

Although the results were incomplete or transient, this study provides a new approach to the problem and opens new perspectives in the prevention of HCV infection after LT.

Prophylactic therapy

There is evidence suggesting a possible role for hepatitis C immune globulin in the prevention of recurrent HCV infection after LT. The prevalence of HCV recurrence after LT was lower in those who received HBIg that presumably contained anti-HCV antibodies (Ab) (prior to 1990, when plasma donors were not screened for the HCV Ab)[123]. Phase I trials with chimpanzees have demonstrated the ability of hepatitis C Ig (human) to decrease hepatic inflammation and to neutralize the HCV antibody, but this effect was not sustained over time[124,125]. Phase I/II human studies have currently been unable to replicate the animal studies[126,127]. Therefore, at present, there is no established role for HCV antibody therapy in the management of liver transplant recipients with HCV.

IMPACT OF GENOMIC MEDICINE ON HCV RECURRENCE

From 2009, single nucleotide polymorphisms (SNPs) near the *IL28B* gene were identified by genome-wide association studies and were associated with SVR or non-response to treatment with PEG-IFN-α and RBV alone or in combination with protease-inhibitors[128-133]. It was estimated that the genotype of these SNPs accounts for approximately 15% of the inter-individual differences in SVR rates after standard treatment in HCV genotype 1 patients[134].

Most recently, a number of studies have analyzed the role of genetic variants of IL-28b in the severity of HCV recurrence and on antiviral treatment response.

Eurich *et al*[135] evaluated only the role of the recipient genotype and reported that IL-28b polymorphism seems to influence the degree of graft inflammation at the biochemical and histological levels. The G-allele has been proposed as a marker for graft inflammation and a pre-

dictor for unfavorable antiviral therapy outcome in HCV-infected LT-population.

Lange *et al*[136], who also investigated the donor genotype, evidenced that response to antiviral therapy was strongly associated with the donor *IL28B* major genotype (T/T) but only weakly with the recipient's *IL28B* genotype[136].

In contrast, other studies have reported that both recipient and donor genotypes seemed to influence the response to Peg-IFN + RBV[137-139].

Furthermore, it has been shown that an unfavorable *IL28B* genotype was associated with more rapid fibrosis, but not with decreased survival[139].

These findings may open new interesting scenarios in the field of recurrence of HCV disease after LT, such as changes in the graft allocation system by determining the *IL28B* genotype of potential donors; this may identify the optimal graft/recipient matching in order to improve the sensitivity to antiviral therapy for HCV infection post-transplantation and therefore improve outcomes.

CONCLUSION

Management of recurrent HCV disease is one of the most challenging problems in the transplant hepatology. Overall excess immunosuppression seems to have an impact on HCV disease progression, although no beneficial immunosuppressive drug has been identified so far. Optimizing the donor selection, with donor age limitations, the exclusion of moderately to severely steatotic livers and the reduction of ischemic times, could be a potential strategy to minimize the severity of HCV recurrence and improve the outcome of HCV positive recipients. Pre-transplant antiviral therapy is limited by low tolerability, low SVR and is indicated in a limited population of transplant candidates.

Post-transplant combination antiviral therapy in those with evidence of recurrent disease is the mainstay of management and has a beneficial effect on virological, biochemical and histological responses in patients with HCV infection post-LT.

In the long term, specifically targeted antiviral therapies that block the replication of HCV, such as HCV protease and polymerase inhibitors, associated with Peg-IFN and RBV, may achieve higher rates of SVR becoming the standard of care.

Future research focusing on the role of prophylactic therapy and immunotherapy are needed in this important patient population.

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