

Review article: the treatment of genotype 1 chronic hepatitis C virus infection in liver transplant candidates and recipients

D. Joshi, I. Carey & K. Agarwal

Institute of Liver Studies, King's College Hospital, London, UK.

Correspondence to:

Dr D. Joshi, Institute of Liver Studies, King's College Hospital, London, SE5 9RS, UK.
E-mail: d.joshi@nhs.net

Publication data

Submitted 28 November 2012
First decision 20 December 2012
Resubmitted 3 February 2013
Accepted 3 February 2013
EV Pub Online 21 February 2013

This uncommissioned review article was subject to full peer-review.

SUMMARY

Background

Recently, the therapeutic landscape with regard to anti-HCV therapy has changed dramatically. The new directly acting anti-virals (DAAs) have demonstrated improved sustained virological response (SVR) compared with pegylated-interferon and ribavirin.

Aim

To examine and present the latest data with regard to anti-viral therapy in genotype 1 HCV-positive transplant candidates and recipients.

Methods

An electronic search using Medline was performed. Search terms included 'HCV, DAA and protease inhibitor' in combination with 'treatment pre-transplantation' and 'treatment post-transplantation'.

Results

Patients with advanced fibrosis and cirrhosis have inferior SVR rates compared with patients with minimal fibrosis. A low accelerating dose regimen (LADR) of pegylated interferon and ribavirin (PR) appears to be a safe therapeutic option. Side effects also appear to be more pronounced in patients with advanced disease. Data from the large registration studies with triple therapy (boceprevir or telaprevir plus PR) demonstrated improved SVR rates even in patients with advanced disease, although virological relapse rates were highest amongst these patients. In transplant recipients, initial data are being reported on the use of triple therapy, and although no SVR data are available, promising results are accruing. The drug–drug interactions appear to be manageable. Side effects in particular anaemia appear to be markedly increased in the post-transplant setting.

Conclusions

The use of the new DAAs in patients with advanced fibrosis/cirrhosis pretransplant and posttransplant appears possible, with manageable side effects and drug–drug interactions, and improved early virological response rates. We recommend that these patients are managed in centres with the appropriate expertise.

Aliment Pharmacol Ther 2013; **37**: 659–671

INTRODUCTION

Hepatitis C virus (HCV) infection is a global epidemic and a leading cause of chronic liver disease.¹ Data from the World Health Organisation (WHO) estimate that 3–4 million individuals are infected with HCV every year.² Currently, chronic HCV is the leading cause of death from liver disease and the leading indication for liver transplantation (LT) in the United States and Western Europe.^{3–5}

Spontaneous clearance of HCV post-LT is rare and re-infection of the liver allograft is universal in individuals with HCV viraemia at the time of transplantation. Compared with other aetiologies, patient and graft survival rates are inferior due to progressive fibrosis driven by HCV recurrence.^{6, 7} Several strategies have therefore emerged to help improve outcomes post-LT including optimal donor, recipient and immunosuppression selection. Another potential strategy is exposure to anti-viral therapy (AVT) pre-LT for those on the transplant waiting list to achieve an undetectable HCV viral load at the time of LT.⁸

This review addresses treatment of HCV in patients with advanced fibrosis or cirrhosis who are transplant candidates, and transplant recipients posttransplant in genotype 1 patients. We highlight important predictors of response, the increased side effect profile and the increasing experience of the use of the new protease inhibitors and directly acting anti-virals (DAAs) both pre- and posttransplant.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched Medline (1 Jan 1966 to 1 September 2012) with the search term 'HCV and protease inhibitor' in combination with 'treatment pre-transplantation' and 'treatment post-transplantation'. Publications were reviewed by DJ and KA, and were selected predominantly from the last 5 years. Given the rapidly evolving landscape with regard to the newer DAAs, we also included abstracts from recent conferences. Older seminal publications were not excluded. Reference lists of articles identified by this search strategy were reviewed. Our reference list was also modified on the basis of comments from peer reviewers.

PRE LIVER TRANSPLANT

Treatment in patients with advanced fibrosis and cirrhosis

Virological response rates are lower in patients with cirrhosis; sustained virological response (SVR) rates ranging

between 40% and 50% for Child-Pugh (CP) class A and between 7 and 26% for CP class C.^{9–12} Poorer SVR rates are also evident in genotype 1 and 4 patients compared with genotype 2 and 3 patients with advanced fibrosis (51% vs. 61%) and cirrhosis (33% vs. 57%).¹² A marked step-wise reduction in SVR is apparent according to fibrosis stage in genotype-1 patients; no fibrosis (70%) vs. cirrhosis (10%), $P < 0.0001$.¹² Irrespective of viral genotype, a rapid virological response (RVR) remains the strongest on treatment predictor of SVR.¹² Although data from the IDEAL study would suggest that treatment with either PEG-IFN alpha 2a or 2b is equally efficacious, more recent data would suggest hypo-responsiveness to PEG-IFN alpha 2b and ribavirin in patients with cirrhosis.^{13, 14}

Treatment of patients with CP-A and early CP-B (score 7) disease can result in attenuation of disease progression, development of hepatocellular carcinoma and potentially end in clinical remission with avoidance for the need for LT altogether. The aim of treating patients with advanced fibrosis or cirrhosis who are listed for LT is to potentially allow the patient to enter transplantation with an undetectable HCV viral load and therefore reduce the chance of recurrence posttransplantation. The latter observation was based on the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Liver Transplant Database study, which demonstrated that patients with lower titres of HCV ($<1 \times 10^6$ viral copies/mL) before transplantation had improved mortality and graft survival.¹⁵ Current EASL guidelines¹⁶ are shown in Table 1. Patients who are listed for LT based on HCC who are not undergoing local-regional therapy should also be considered for AVT. AVT is poorly tolerated in patients with

Table 1 | European Association for the Study of the Liver (EASL) guidelines for treatment of chronic hepatitis C virus infection in patients with cirrhosis¹⁶

Child Pugh – A
Strongly consider treatment
Strongly consider use of growth factors
Indicated in patients whom indication for liver transplantation is hepatocellular carcinoma
Child Pugh – B
Treatment offered on individual basis
Recommend use of Norfloxacin prophylaxis in patients with ascites
Low accelerating dosing regimen recommended
Strongly consider use of growth factors
Child Pugh – C
Treatment contraindicated

advanced fibrosis/cirrhosis and can precipitate hepatic decompensation. Long-term, maintenance therapy with PEG-IFN in patients with advanced fibrosis or cirrhosis who fail to achieve an SVR with conventional therapy is currently not advocated.^{17, 18}

Treatment on the transplant waiting list

Initial data with the use of interferon (IFN) mono-therapy in small cohorts of patients demonstrated that AVT was feasible in cirrhotic patients albeit with an increased side effect profile.^{19–22} Studies evaluating the role of AVT in patients with cirrhosis and undergoing liver transplantation are summarised in Table 2.

Patients who present with a living donor represent an ideal patient group in whom AVT can be timed so that ideally these patients enter transplantation with an undetectable HCV viral load. Given the poorer tolerability of AVT amongst cirrhotic patients and the possibility of hepatic decompensation, the concept of a low accelerating dose regimen (LADR) was introduced.⁸ An LADR essentially involves commencing patients on reduced doses of pegylated interferon (PEG-IFN) and ribavirin (PR) and then incrementing doses every 2 weeks to achieve maximally tolerated or target standard doses.

A recent multi-centre, randomised study further evaluated the efficacy and safety of pretransplant AVT for the prevention of HCV recurrence posttransplant.²³ Although this study was not limited to genotype 1 patients only, a total of 59 patients listed for either living donation or HCC with MELD exception underwent treatment with an LADR and were compared with 20 untreated patients. A total of 57 patients subsequently underwent transplantation (44 treated and 13 controls): 26 (59%) treated patients had undetectable HCV RNA at the time of transplant with 11 (42%) patients demonstrating HCV RNA negativity 24 weeks posttransplant; 13 (50%) patients subsequently relapsed posttransplantation. Predictors of an undetectable HCV RNA 12 weeks posttransplantation included PR treatment duration >16 weeks, but not viral genotype. No increase in serious adverse events (SAEs) was noted in treated group (68% vs. 55%, $P = 0.3$), although the number of SAEs per patient was higher (2.7 vs. 1.3, $P = 0.003$).²³

Side effects

Data available would suggest a significant side effect profile in patients with advanced fibrosis or cirrhosis undergoing AVT.^{8, 19–22} Side effects are more common in patients with CP class C and MELD >18. In addition, dose reductions are more common in patients with

	Total screened (n)	Treated (n)	Anti-viral therapy	Duration (months)	Side effects (n)	EOTR n (%)	SVR	Transplanted (n)	HCV RNA negative at time of transplant (n)	HCV RNA negativity post LT n (%)
Crippin <i>et al.</i> , 2002	32	15	IFN + R	2	20 × SAE 1 × death	5/33	–	2	1	0
Forns <i>et al.</i> , 2003	50	30	IFN + R	3	26 × SAE	9/30%	–	30	6	6/20%
Thomas <i>et al.</i> , 2003	27	20	IFN	14	–	12(60)	–	20	12	4/20%
Everson <i>et al.</i> , 2005	–	124	IFN + R (LADR)	6–12	15 × SAE 4 × death	G1: 26/30% Non-G1: 57/46%	G1: 11/13% Non-G1: 19/50%	47	15	12/26%
Carrión <i>et al.</i> , 2009	122	51	PEG-IFN + R	3	28 × SAE 4 × death	15/29%	–	43	15	10/20%
Everson <i>et al.</i> , 2012	145	59	PEG-IFN + R (LADR)	3–12	27 × SAE 7 × sepsis 9 × death	–	*25/59%	44	26	11/25%

IFN, interferon; R, ribavirin; PEG-IFN, pegylated interferon; LADR, low accelerating dose regimen; SAE, serious adverse event; EOTR, end of treatment response; SVR, sustained virological response; LT, liver transplantation; G1, genotype 1.

* Negative HCV RNA at the time of liver transplantation.

cirrhosis. The development of neutropenia, thrombocytopenia along with anaemia is common, necessitating dose reductions in both PR doses, although the majority of tolerability issues relate to the pegylated interferon component. A retrospective case-control study also demonstrated an increased incidence of bacterial infections particularly in CP-B and -C patients undergoing AVT (17 vs. 3 episodes, $P = 0.002$).²² In the same study, an increased incidence of spontaneous bacterial peritonitis in patients undergoing AVT not receiving norfloxacin prophylaxis was also demonstrated.²² The incidence of hepatic decompensation in patients with compensated cirrhosis is between 0% and 3%, although these data may be an underestimation due to patient selection within clinical trials.^{24–26}

Triple therapy; protease inhibitor + pegylated interferon and ribavirin

In 2011, the first generation of protease inhibitors (PI), boceprevir and telaprevir, were released and approved for patients with genotype 1 HCV disease only. Boceprevir is a linear peptidomimetic keto-amide serine protease inhibitor that reversibly binds to the HCV nonstructural 3 (NS3) active site whilst telaprevir inhibits the NS3/4A HCV protease.^{27, 28} Triple therapy (PI + PR) is now

regarded as standard of care for genotype 1 patients. Overall SVR rates in treatment-naïve patients were increased significantly to between 68% and 75% and in previously treatment-experienced patients to between 59% and 88%.^{29–33}

Protease inhibitors in treatment-naïve genotype 1 patients with advanced fibrosis or cirrhosis

The SPRINT-2 (serine protease inhibitor therapy 2) trial was a phase III study conducted in treatment-naïve patients using boceprevir.²⁹ A total of 1097 patients were included, 100 patients (9%) having either advanced fibrosis ($n = 47$) or cirrhosis ($n = 53$). All patients received a lead-in of PR for 4 weeks before being randomised into 3 groups: Group 1, PR for 44 weeks; Group 2 (response-guided therapy group, RGT), boceprevir and PR for 24 weeks (those with detectable HCV RNA between 8 weeks and 24 weeks received PR for further 20 weeks); and Group 3, boceprevir and PR for 44 weeks. Overall, SVR rates were higher in the boceprevir treatment groups in particular amongst patients with minimal fibrosis, although a benefit was evident in patients with either advanced fibrosis or cirrhosis (Figure 1). Relapse rates were, however, higher amongst patients with advanced fibrosis or cirrhosis compared with patients

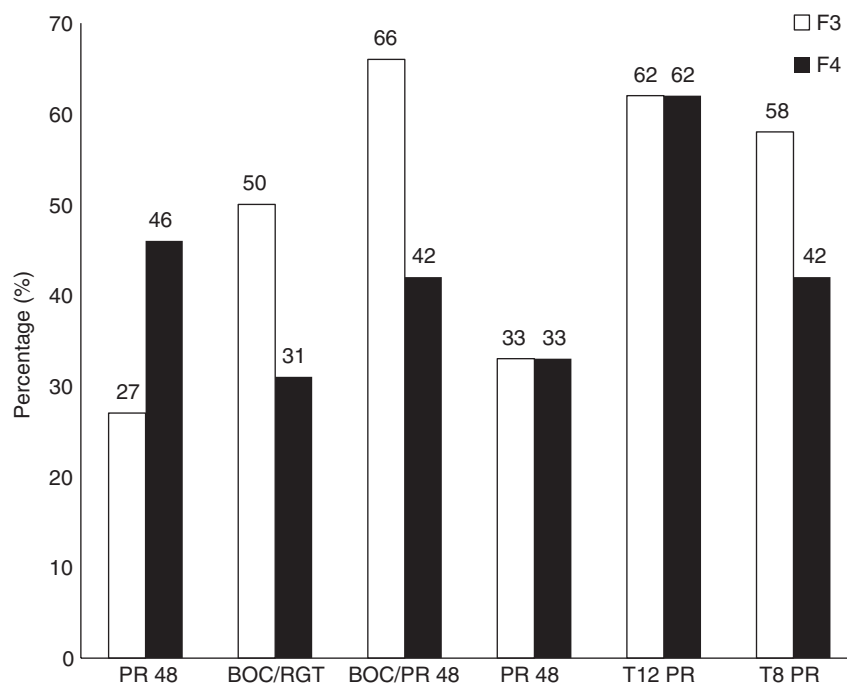


Figure 1 | Sustained virological response rates with Boceprevir and Telaprevir in treatment-naïve genotype-1 patients with chronic hepatitis C infection with advanced fibrosis and cirrhosis. PR, pegylated interferon and ribavirin; BOC/RGT, boceprevir with response-guided therapy; T12, telaprevir 12 weeks; T8, telaprevir 8 weeks; F3, fibrosis stage 3; F4, fibrosis stage 4 (cirrhosis). Modified from Poordad et al.²⁹ and Jacobson et al.³⁰

with minimal fibrosis (12–18% vs. 9%). The absence of cirrhosis was identified as a baseline predictor of SVR with boceprevir and PR (OR: 2.5, 95% CI: 1.4–4.6, $P = 0.003$). On treatment, viral kinetics remained an important predictor of SVR; RVR (undetectable HCV RNA at week 8) allowed shortened treatment duration amongst patients with minimal fibrosis only. An RVR, however, was less common amongst patients with advanced fibrosis or cirrhosis. In conclusion, the authors recommended that treatment-naïve patients with advanced fibrosis or cirrhosis should receive a fixed duration of therapy (boceprevir and PR for 48 weeks in total).²⁹

The ADVANCE study evaluated the efficacy of telaprevir in addition to PR in 1088 patients.³⁰ Patients were again randomised to 3 groups: group 1, PR for 48 weeks; group 2, telaprevir and PR for 12 weeks followed by 12 weeks of PR (if HCV RNA negative at weeks 4 and 12) or PR for 36 weeks if HCV RNA was detectable at week 4 or week 12); and group 3; telaprevir and PR for 8 weeks and then placebo and PR for 4 weeks followed by either 12 or 36 weeks of PR. SVR rates were significantly higher in those who received telaprevir and PR compared with PR alone. This remained true also amongst patients with advanced fibrosis and cirrhosis (Figure 1). The ILLUMINATE study, which included 540 patients, aimed to establish the role of an extended RVR (eRVR; HCV RNA negative at weeks 4 and 12) in guiding treatment duration.³³ An eRVR was less frequent amongst patients with advanced fibrosis and cirrhosis. Patients who received telaprevir for 12 weeks and PR for 48 weeks who achieved an eRVR had better SVR rates (94%, 11 from 12) compared with those who received telaprevir for 12 weeks and PR for 24 weeks (62%, 11 from 18) who had also achieved an eRVR. Therefore, treatment-naïve patients with advanced fibrosis undergoing triple therapy with telaprevir should receive 48 weeks of treatment.

Protease inhibitors in previously treated genotype 1 patients with advanced fibrosis or cirrhosis

The RESPOND-2 study evaluated the use of boceprevir in previously treated patients.³¹ An important observation to be made is that only responder-relapsers and partial responders (more than $2\log_{10}$ IU/mL decrease in HCV RNA level from baseline at 12 weeks of therapy, but detectable HCV RNA at weeks 12–24) were included. Null responders (less than $2\log_{10}$ IU/mL decrease in HCV RNA level from baseline at 12 weeks of therapy) were not included. Patients were once again

randomised to either PR alone, boceprevir and PR (RGT group) or boceprevir and PR (fixed duration group). Overall SVR rates were increased in the boceprevir receiving groups by 42% compared with PR alone in patients with F3/F4, and by 44% in patients with minimal fibrosis.³¹ Improved SVR rates were observed amongst cirrhotic patients compared with noncirrhotic patients who received boceprevir and PR for 48 weeks (Figure 2). Relapse rates were once again higher amongst patients with advanced fibrosis or cirrhosis compared with those with minimal fibrosis (21% vs. 11%).

The REALIZE trial included previously treated patients including previous null responders.³² Groups were similar to the ADVANCE study. SVR rates were considerably higher amongst those who received telaprevir compared with PR alone across all fibrosis stages; 75% vs. 22% minimal fibrosis, 47% vs. 10% cirrhosis. Previous responder relapsers who received telaprevir had the highest SVR rates compared with previous partial responders and null responders (Figure 3). Relapse rates were highest amongst cirrhotic patients once again, especially amongst those with previous partial response or null response.

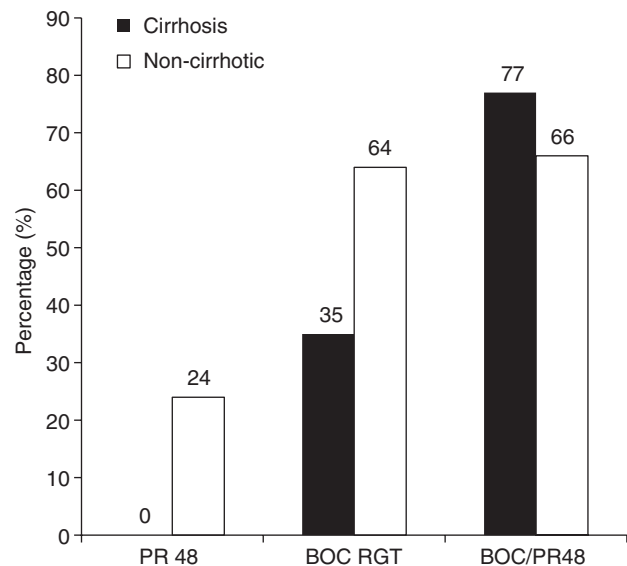


Figure 2 | Sustained virological response rates with Boceprevir in treatment-experienced patients with chronic hepatitis C infection (cirrhotic vs. noncirrhotic). PR 48, pegylated interferon and ribavirin 48 weeks; BOC/RGT, Boceprevir and PR response-guided therapy; BOC/PR 48 weeks, Boceprevir and pegylated interferon 48 weeks. Modified from Bacon et al.³¹

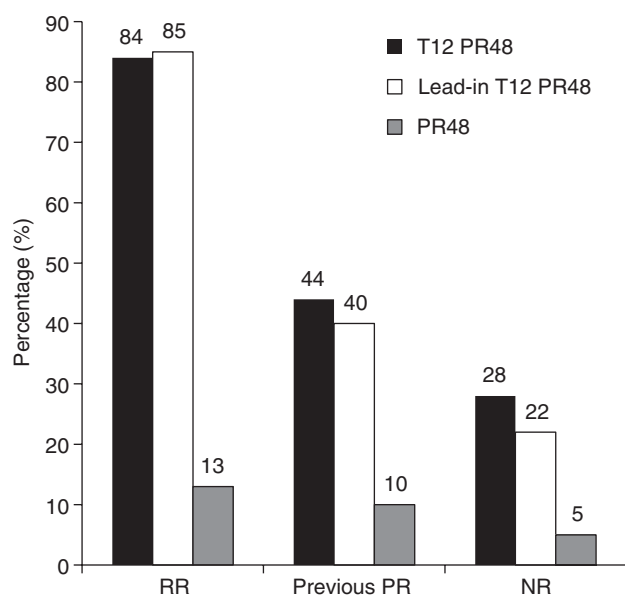


Figure 3 | Sustained virological response rates with Telaprevir in treatment-experienced patients with chronic hepatitis C infection with advanced fibrosis/cirrhosis according to previous treatment response. T12 PR48, telaprevir 12 weeks + pegylated interferon and ribavirin 48 weeks; PR 48; pegylated interferon and ribavirin 48 weeks; RR, responder relapse; PR; partial responder; NR, null responder. *Modified from Zeusem et al.*³²

Data from the CUPIC (Compassionate Use of Protease Inhibitors in Viral C Cirrhosis) cohort have demonstrated a higher rate of serious adverse events (49% telaprevir; 38% boceprevir) and a high rate of discontinuation due to severe adverse events (15% telaprevir; 7% boceprevir) compared with phase III trials.³⁴ Grade 2 anaemia (HB 8.0 to <10.0 g/dL) occurred in 20% of patients receiving telaprevir and in 23% receiving boceprevir, whilst grade 3/4 anaemia (HB <8.0 g/dL) occurred in 10% of patients on telaprevir or boceprevir. EPO was required in nearly two-thirds of patients receiving either telaprevir or boceprevir. However, despite the increased side effect profile, the interim analysis on an intention-to-treat basis demonstrated high rates of virological response after 16 weeks of treatment [71% (177/251) of patients on telaprevir and 61% (89/146) patients had undetectable HCV RNA].³⁴ A further study in 20 patients who were awaiting liver transplantation with the use of predominately telaprevir demonstrated that 44% had undetectable HCV viral load at 4 weeks rising to 71% at 12 weeks.³⁵ Triple therapy was discontinued early in 25% of patients with 10% decompensating on treatment.³⁵

Side effects with telaprevir and boceprevir

Common reported side effects with boceprevir included anaemia and dysgeusia (metallic taste), whilst rash was observed in over 50% of patients taking telaprevir. Side effects to PIs appear to be more common amongst patients with cirrhosis.^{29–33} Anaemia should be managed initially by a reduction in the ribavirin dose.³⁶ A nested study within a randomised trial of genotype 1 HCV treatment-naïve patients demonstrated that ribavirin dose reduction or the addition of EPO led to similar SVR rates in patients receiving Boceprevir (71% SVR in both groups).³⁷ The development of anaemia (HB <10 g/dL) in fact appears to be a positive predictor of SVR with boceprevir only.³⁸ The dose of telaprevir or boceprevir should not be reduced or stopped and then restarted. In addition, telaprevir and boceprevir should not be continued as mono-therapy without PR.

At present, there are minimal data on the use of triple therapy and the safety in patients with evidence of borderline decompensated disease or HCC is unknown. The use of triple therapy in patients with cirrhosis remains high risk especially in those with evidence of decompensation. Several deaths have been reported even with dose reductions and close monitoring mainly related to severe infection associated with more advanced cirrhosis (low albumin levels) and diabetes.³⁴ We recommend early referral and evaluation for liver transplantation in cirrhotic patients being considered for triple therapy. The use of prophylaxis against spontaneous bacterial peritonitis in patients with ascites and borderline liver function or portal hypertension should be considered.

POST LIVER TRANSPLANT

HCV recurrence post-LT is influenced by a combination of donor, recipient, viral and immunosuppression factors.^{39–45} Overall, fibrosis rates are accelerated compared with patients pretransplant, resulting in cirrhosis, graft loss and consideration for re-transplantation.^{6, 46, 47} Fibrosing cholestatic hepatitis (FCH) is a rare but severe, aggressive form of HCV recurrence.⁴ FCH is associated with a rapid progression to graft failure.⁴⁸ Although AVT has been used in patients with FCH, reported outcomes are poor.⁴⁹ At present, AVT remains the only viable therapeutic strategy, which can alter fibrosis progression.^{50, 51} The benefits of achieving an SVR are clear; improvement in liver fibrosis, lower probability of decompensation and a lower cumulative mortality post-transplantation.^{52, 53}

Two principal strategies have been adopted: pre-emptive treatment and treatment following evidence of

histological recurrence. The current 'standard of care' in the posttransplant period is PR for 48 weeks irrespective of viral genotype.

Preemptive treatment

Preemptive treatment of HCV recurrence post-LT is commenced immediately posttransplantation and is based on the hypothesis that virological recurrence is universal in all patients. The obvious advantages with this strategy are that HCV RNA levels will be at their lowest and liver fibrosis will be minimal.

Studies to date that have adopted this treatment strategy are both limited and heterogeneous (genotype 1 and nongenotype 1 patients), some using interferon-alpha mono-therapy, whilst others have used pegylated interferon-alpha in combination with ribavirin.^{54–58} Two randomised, prospective studies that used interferon-alpha mono-therapy, beginning 2 weeks after transplantation, clearly demonstrated that those treated were less likely to develop a recurrent hepatitis than patients who were not treated.^{54, 55} Neither study, however, was able to demonstrate any survival benefit in patients who received interferon treatment. In a study of 36 patients, using both interferon-alpha and oral ribavirin for 12 months, the authors were able to demonstrate HCV-RNA clearance in 12 patients (33%).⁵⁶ An important observation made by this study was that HCV-RNA clearance was more likely to be achieved by those with lower baseline HCV RNA levels.

More recent studies have used PR and demonstrated SVRs between 8% and 18%.^{58, 59} Although the SVR rates were considerably lower than those previously reported, the key message from one of these studies was that preemptive AVT was only applicable in 51% of patients and the desirable >80% treatment dose and >80% treatment duration was only achieved by a small number of patients (14%).⁵⁸ Cytopenias, especially anaemia, post-operative complications and severe debilitation relating to the severity of illness pretransplantation all limit the applicability of AVT.

Treatment of established hepatitis C recurrence

Studies assessing the efficacy of AVT once histological evidence of hepatitis C recurrence has been established are more numerous and reflect the preferred setting to commence anti-HCV therapy. The reasons for this seem to be multifactorial: a recuperated patient with less comorbid or postsurgical concerns, reduced risk of acute cellular rejection, better graft function and lower doses of immunosuppression. Earlier studies that evaluated this

strategy reported SVR rates of between 12% and 24% with pegylated interferon mono-therapy and PR.^{59, 60} In both studies, however, there was a wide variation in median time from transplantation to treatment (6–96 months) and grade of baseline fibrosis demonstrating the heterogeneity of the patients groups.

Most centres institute AVT once histological evidence of HCV is established, usually more than 12 months posttransplantation. To establish the optimal timing of when to begin treatment, one study attempted to extrapolate the experience and success of treating acute HCV in pretransplant cohorts and treat patients in the post-transplant period as soon as acute HCV was detected.^{61, 62} Inclusion criteria included persistent ALT elevation, HCV-RNA positivity, histological evidence of lobular hepatitis consistent with recurrent HCV and no evidence of acute or chronic rejection, biliary obstruction or ischaemic changes. Twenty-five patients eventually underwent treatment with the interval between LT and histological evidence of HCV recurrence of approximately 4 months. Fourteen patients (58%) had an EOTR and 8 (35%) had an SVR. Although side effects were common, asthenia and muscle pain the most frequent, no patient discontinued his/her interferon treatment.

More recent studies have used PEG-IFN alpha-2b (1.5 mcg/kg) or alpha-2a (180 µg) and ribavirin 800–1200 mg.^{52, 60, 62–65} (Table 3). Reported SVR rates for all genotypes range between 8% and 45%.^{66–68} SVR rates for genotype 1 patients, however, are considerably lower ranging between 13% and 33% only.⁶⁶ Once again, the study cohorts were heterogeneous with wide variation in the time from LT to the start of treatment and the percentage of patients with advanced fibrosis.^{52, 60, 63–65, 69} Treatment appears to be more efficacious when the histological recurrence of HCV is mild; 48% SVR in patients with mild HCV recurrence vs. 19% SVR in patients with severe HCV recurrence.⁶⁵ One consistent finding, however, amongst these studies was the numbers of patients who discontinued treatment early, and their poor tolerability. Two studies addressed the potential benefit of long-term maintenance anti-viral therapy, but failed to demonstrate any clear benefit.^{70, 71}

There is only one prospective, multi-centre randomised study published that has attempted to determine which treatment strategy is better and safest.⁷² The PHOENIX (Pegasys and Copegus Administered After Liver Transplantation for Hepatitis C) study conducted in North America reported SVR rates of 22% in the preemptive group, but with discontinuation rates of greater than 40% predominately due to haematological side

Table 3 Studies evaluating treatment outcomes with pegylated interferon and ribavirin for established recurrent HCV post liver transplantation									
	Total transplanted (n)*	Treated (n)	N (%) Genotype 1	SVR	Duration of Rx (weeks)	Time to treatment post LT (months)	N (%) with advanced fibrosis	N (%) discontinued secondary to side effects	
Dumortier et al., 2004	97	20	16 (80)	45% (9/20)	48	28 (median)	–	14 (20)	
Castells et al., 2005	83	24	24 (100)	–	24	3.8 ± 2.2	–	–	
Oton et al., 2006	171	55	50 (91)	G1 – 40% Overall – 44%	48 weeks – G1 24 weeks – G2/3	63 (mean)	18 (33)	13 (24)	
Angelico et al., 2007	–	42†	35 (83)	36%	48	44 (median) range 12–96	–	12 (29)	
Carrion et al., 2007	140	81	73 (90)	33% (18/54)	24	15	27(33)	21/54 (40)	
Picciotto et al., 2007	123	61	53 (87)	28% (17/61)	48 weeks – G1 24 weeks – G2	25 (median) Range 3–131	28 (46)	8 (15)	
Hanouneh et al., 2008	–	53	42 (79)	35% (19/53)	48	15 (median)	10 (19)	14 (26)	
SVR, sustained virological response; Rx, treatment; LT, liver transplant; G1, genotype 1.									
* Total number of patients transplanted during study period.									
† Compared pegylated interferon and ribavirin vs. pegylated interferon role.									

effects.⁷² In the same study, those treated for established recurrence had SVR rates of 21%. This study was unable to delineate which strategy was optimal for the treatment of recurrent HCV infection posttransplantation, primarily due to small study numbers. However, a repeat of this study with the addition of the DAAs may be able to establish the optimal treatment strategy but may also reveal significant tolerability issues.

The overall poorer SVR rates reported in patients posttransplant for HCV are likely due to a combination of factors: (i) the high percentage of patients with genotype 1 disease, (ii) high percentage of patients with a previous poor response to AVT, (iii) higher baseline HCV viral loads, (iv) increased incidence of side effects leading to significant dose reductions or discontinuation, (v) the interaction with immunosuppression and (vi) the lack of use of growth factors to support bone marrow function.

Predictors of sustained virological response

Predictors of SVR can be divided into pre-treatment variables and on-treatment variables. Pre-treatment factors associated with an SVR include a low baseline HCV viral-load, HCV RNA <800 000 IU/mL, younger recipient age, nongenotype 1 disease, shorter length between LT and commencing treatment, donor age <50 years, low baseline bilirubin levels and mild fibrosis^{64, 66–69, 73} (Table 4). On-treatment predictors include an EVR and a RVR.

The IL-28B genotype has also been evaluated in the posttransplant setting.^{44, 45, 74, 75} The favourable CC (rs12979860) and TT (rs8099917) genotypes are both associated with SVR ($P < 0.005$).^{44, 45, 75} Both recipient and donor IL-28B genotype have been evaluated with

Table 4 | Pre-treatment and on-treatment predictors of sustained virological response post liver transplantation with pegylated interferon and ribavirin

Pre-treatment

Low baseline HCV viral load (<800 000 IU/mL)

Younger recipient age

Younger donor age

Nongenotype-1 disease

Shorter duration between liver transplantation and anti-viral treatment

Mild fibrosis (F < 2)

rs12979860 IL28B CC genotype

On-treatment

Rapid virological response (RVR)

Early virological response (EVR)

one study suggesting a more dominant role for the donor IL-28B genetic polymorphisms on treatment outcome.⁴⁵

Available data suggest that the use of ciclosporin over tacrolimus is associated with an increased chance of SVR (RR: 2.0, CI: 1.2–3.5, $P = 0.02$) and a reduced risk of relapse (RR: 0.4, CI: 0.2–0.9, $P = 0.02$).^{76, 77, 77, 78} Suggested mechanisms include the direct anti-viral effect of ciclosporin demonstrated *in vitro* and the inhibition of NS5B binding to cyclophilin B.^{79, 80} Results from ReViS-TC study demonstrated that the use of ciclosporin (RR: 1.972, $P = 0.02$) and a longer treatment duration of AVT (RR: 1.2, $P < 0.001$) were predictive of a SVR.⁷⁶

Directly acting anti-viral agents post liver transplantation

The use of DAAs in the posttransplant setting in patients with genotype 1 HCV disease has been limited. Early pharmacokinetic data tempered expectations in the LT group. Data on the use of telaprevir in healthy volunteers resulted in a significant increase in ciclosporin (5-fold) and tacrolimus levels (70-fold) due to the inhibition of the P450 3A cytochrome.⁸¹ Drug–drug interactions remain a significant clinical issue. In patients with genotype 2/3 disease, we would recommend the use of PR according to their virological response and kinetics.

A recent study reported their experience with the use of boceprevir in 5 patients post-LT.⁸² A 50% reduction in ciclosporin dose and up to 80% reduction in tacrolimus dose were required, steady levels being achieved by 4 days. Follow-up was limited to treatment week 12, but all patients achieved a virological response (≥ 2 log drop) during this time. Anaemia was the commonest side effect with all patients requiring erythropoietin. Although the numbers are small, this study demonstrates ‘proof of concept’ that the newer DAAs can be used safely with encouraging virological response rates.

Individual centres are now reporting their experience with the use of the new protease inhibitors in the post-transplant period.^{83–90} Switching patients to ciclosporin appears to be common due to smaller variations in dosing although tacrolimus levels appear to be manageable also.^{83, 85, 88–91} The use of a lead in phase even with telaprevir appears to be gaining popularity in the post-transplant period as it allows the clinician to make an assessment of tolerability. The number of patients being treated by these individual centres is small; and at present, only early virological response data are reported (EVR and RVR data). No SVR data are currently available, but early reported viral responses seem promising.

At present, the data are based on mono-centric experiences and specific recommendations are difficult to make. Furthermore, no data are currently available regarding the development of viral resistance and its impact in the posttransplant period. A phase IIb study of the use of telaprevir (REPLACE) in stable, noncirrhotic liver transplant patients with genotype 1 disease is currently on-going and recruiting.⁹²

Case reports are also emerging of the use of the newer DAAs in the posttransplant period. A recent publication reported the successful use of Daclatasvir (NS5A complex inhibitor) in combination with PR in a patient who had undergone re-transplantation following the development of FCH.⁹³ In the said case, the patient with genotype 1b disease only received a total of 24 weeks of daclatasvir and PR and remained HCV RNA-negative 32 weeks after treatment cessation. The same group has also reported the use of daclatasvir in combination with GS-7977 (a NS5A polymerase inhibitor) without the use of PR in a patient with severe HCV recurrence.⁹⁴ There is currently an on-going phase 2 study investigating GS-7977 and ribavirin for 24 weeks in patients with recurrent HCV posttransplantation.⁹⁵

Side effects and tolerance

Reduced tolerability due to fatigue, asthenia, pyrexia and the development of cytopenias, in particular anaemia, is well described. Side effects appear to be more prominent in patients with a severe hepatitis.⁶⁵ On multivariate analysis, factors associated with the development of significant anaemia (>5 g/dL) with the use of PR only included estimated creatinine clearance (RR: 0.951, CI: 0.925–0.978, $P < 0.001$), the use of mycophenolate mofetil (RR: 5.3, CI: 1.4–20.0, $P = 0.01$), ciclosporin (RR: 3.5, CI: 1.4–8.7, $P = 0.008$), baseline HCV viral load $>600\,000$ IU/mL (RR: 4.8, CI: 1.7–13.5, $P = 0.003$) and baseline haemoglobin values (RR: 3.0, CI: 1.9–4.7, $P = 0.001$).⁹⁶

The use of interferon can be associated with the development of immune-mediated graft dysfunction (IGD) – an umbrella term for acute rejection (AR), chronic rejection (CR) and plasma cell hepatitis (PCH).^{68, 97–99} Certainly, in the preemptive treatment approach, concerns following the introduction of interferon so soon after transplantation are due to the risk of precipitating ACR or an episode of sepsis. The development of a PCH is associated with poor outcomes.^{97, 100} In a recent study, evidence of a PCH on a pre-treatment biopsy was the most common finding in patients who developed IGD and appears to be an important risk factor for the

development of IGD.¹⁰¹ Other risk factors for IGD included previously treatment-naïve to IFN-based therapy, use of PEG-IFN alpha - 2a, a high pre-treatment alkaline phosphatase and a reduction in immunosuppression prior to commencing AVT.¹⁰¹ The risk of ACR precipitated by treatment overall, appears to be low (0–5%).^{62, 64}

An increased side effect profile has also been reported with the new protease inhibitors in particular anaemia requiring the combination of ribavirin dose reduction, the use of haematological growth support factors and/or blood transfusion.^{82, 83, 86, 87} In one study, 93% of patients required EPO and 14% required blood transfusions.⁸² Skin rashes, anorectal complaints and dysgeusia have also been reported. Concerns regarding possible interactions between the protease inhibitors and CNIs led to one study hospitalising all patients prior to the introduction of the protease inhibitors.⁸² Fold changes of between 2 and 4 in ciclosporin doses have been reported in contrast to much higher fold changes associated with tacrolimus (20–40)^{82, 83, 86, 91} These findings would therefore suggest that ciclosporin dosing maybe easier and less problematic to manage when using telaprevir or boceprevir posttransplantation. Infectious complications, hepatic decompensation and one death secondary to sepsis and multi-organ failure have been reported by one group.⁸⁶

CONCLUSIONS

Treatment of recurrent HCV post-LT begins in the pre-transplant period. Although SVR rates in cirrhotic patients with PR are poor, results with the new PIs in combination with PR have already demonstrated encour-

aging, improved SVR rates. Given the rapidly changing anti-HCV therapeutic landscape and the potential use of interferon-free regimens, SVR rates will undoubtedly continue to improve. Studies are currently on-going investigating the role of DAAs in combination with ribavirin irrespective of viral genotype pretransplant and its direct effect on preventing HCV recurrence posttransplant.¹⁰² These newer pan-genotypic therapies with improved SVR rates and better tolerability will potentially result in fewer HCV patients coming forward as liver transplant candidates and also result in improved mortality and morbidity posttransplantation. Patients with compensated cirrhosis who are listed for liver transplantation should have a trial of AVT. Posttransplantation, patients with established histological evidence recurrence ($F \geq 2$) should be treated early and aggressively. The use of PIs in posttransplant period appears to be feasible in experienced centres, although meticulous attention towards immunosuppression doses and the development of side effects is required. The next generation of DAAs will undoubtedly continue to improve our SVR rates in the pre- and posttransplant period.

AUTHORSHIP

Guarantor of the article: Dr Kosh Agarwal.

Author contributions: DJ devised, wrote and edited the article. IC edited the article. KA supervised and edited the article. All authors read and approved the final manuscript.

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

REFERENCES

- Williams R. Global challenges in liver disease. *Hepatology* 2006; **44**: 521–6.
- World Health Organisation. Available at: <http://www.who.int>. Accessed September 1, 2012.
- Kim WR. The burden of hepatitis C in the United States. *Hepatology* 2002; **36**: S30–4.
- Wiesner RH, Sorrell M, Villamil F. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. *Liver Transpl* 2003; **9**: S1–9.
- Adam R, McMaster P, O'Grady JG, *et al.* Garcia Valdecasas JC, Berenguer J, Jaek D, Moreno GE. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. *Liver Transpl* 2003; **9**: 1231–43.
- Gane EJ, Portmann BC, Naoumov NV, *et al.* Long-term outcome of hepatitis C infection after liver transplantation. *N Engl J Med* 1996; **334**: 815–820.
- Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002; **122**: 889–96.
- Everson GT, Trotter J, Forman L, *et al.* Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. *Hepatology* 2005; **42**: 255–62.
- Fried MW, Shiffman ML, Reddy KR, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975–982.
- Manns MP, McHutchison JG, Gordon SC, *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958–65.
- Hadziyannis SJ, Sette H Jr, Morgan TR, *et al.* Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized

- study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346–55.
12. Bruno S, Shiffman ML, Roberts SK, *et al.* Efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in hepatitis C patients with advanced fibrosis and cirrhosis. *Hepatology* 2010; **51**: 388–97.
 13. McHutchison JG, Lawitz EJ, Shiffman ML, *et al.* Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; **361**: 580–593.
 14. Prati GM, Aghemo A, Rumi MG, *et al.* Hyporesponsiveness to PegIFNalpha2B plus ribavirin in patients with hepatitis C-related advanced fibrosis. *J Hepatol* 2012; **56**: 341–7.
 15. Charlton M, Seaberg E, Wiesner R, *et al.* Predictors of patient and graft survival following liver transplantation for hepatitis C. *Hepatology* 1998; **28**: 823–30.
 16. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2011; **55**: 245–64.
 17. Di Bisceglie AM, Stoddard AM, Dienstag JL, *et al.* Excess mortality in patients with advanced chronic hepatitis C treated with long-term peginterferon. *Hepatology* 2011; **53**: 1100–8.
 18. Di Bisceglie AM, Shiffman ML, Everson GT, *et al.* Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N Engl J Med* 2008; **359**: 2429–41.
 19. Thomas RM, Brems JJ, Guzman-Hartman G, Yong S, Cavaliere P, Van Thiel DH. Infection with chronic hepatitis C virus and liver transplantation: a role for interferon therapy before transplantation. *Liver Transpl* 2003; **9**: 905–15.
 20. Crippin JS, McCashland T, Terrault N, Sheiner P, Charlton MR. A pilot study of the tolerability and efficacy of antiviral therapy in hepatitis C virus-infected patients awaiting liver transplantation. *Liver Transpl* 2002; **8**: 350–5.
 21. Forns X, Garcia-Retortillo M, Serrano T, *et al.* Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. *J Hepatol* 2003; **39**: 389–96.
 22. Carrion JA, Martinez-Bauer E, Crespo G, *et al.* Antiviral therapy increases the risk of bacterial infections in HCV-infected cirrhotic patients awaiting liver transplantation: a retrospective study. *J Hepatol* 2009; **50**: 719–28.
 23. Everson GT, Terrault NA, Lok AS, *et al.* A randomized controlled trial of pretransplant antiviral therapy to prevent recurrence of hepatitis C after liver transplantation. *Hepatology* 2012 [Epub ahead of print].
 24. Di MV, Almasio PL, Ferraro D, *et al.* Peg-interferon alone or combined with ribavirin in HCV cirrhosis with portal hypertension: a randomized controlled trial. *J Hepatol* 2007; **47**: 484–91.
 25. Roffi L, Colloredo G, Pioltelli P, *et al.* Pegylated interferon-alpha2b plus ribavirin: an efficacious and well-tolerated treatment regimen for patients with hepatitis C virus related histologically proven cirrhosis. *Antivir Ther* 2008; **13**: 663–73.
 26. Giannini EG, Basso M, Savarino V, Picciotto A. Predictive value of on-treatment response during full-dose antiviral therapy of patients with hepatitis C virus cirrhosis and portal hypertension. *J Intern Med* 2009; **266**: 537–46.
 27. Venkatraman S, Bogen SL, Arasappan A, *et al.* Discovery of (1R,5S)-N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide (SCH 503034), a selective, potent, orally bioavailable hepatitis C virus NS3 protease inhibitor: a potential therapeutic agent for the treatment of hepatitis C infection. *J Med Chem* 2006; **49**: 6074–86.
 28. Lin K, Perni RB, Kwong AD, Lin C. VX-950, a novel hepatitis C virus (HCV) NS3-4A protease inhibitor, exhibits potent antiviral activities in HCV replicon cells. *Antimicrob Agents Chemother* 2006; **50**: 1813–22.
 29. Poordad F, McCone J Jr, Bacon BR, *et al.* Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195–206.
 30. Jacobson IM, McHutchison JG, Dusheiko G, *et al.* Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364**: 2405–16.
 31. Bacon BR, Gordon SC, Lawitz E, *et al.* Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1207–17.
 32. Zeuzem S, Andreone P, Pol S, *et al.* Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; **364**: 2417–28.
 33. Sherman KE, Flamm SL, Afdhal NH, *et al.* Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011; **365**: 1014–24.
 34. Hezode C, Dorival C, Zoulim F, *et al.* Safety and efficacy of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in 455 cirrhotic non responders. Week 16 analysis of the French early access program (ANRS CO20-CUPIC) in real-life setting. *Hepatology* 2012; **56**: No. 4(S). Abstract 51, 217A.
 35. Verna EC, Terry N, Lukose T, *et al.* High early response rates with protease inhibitor triple therapy in a multicenter cohort of HCV infected patients awaiting liver-transplantation. *Hepatology* 2012; **56**: No. 4(s). Abstract 52, 218A.
 36. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; **54**: 1433–44.
 37. Poordad F, Lawitz E, Reddy K, *et al.* A randomised trial comparing ribavirin dose reduction versus erythropoietin for anaemia management in previously untreated patients with chronic hepatitis C receiving boceprevir plus peginterferon/ribavirin. *J Hepatol* 2012; **56**: S549–60. Abstract 1419.
 38. Sulkowski MS, Poordad F, Manns MP, *et al.* Anaemia during treatment with peginterferon alfa-2b/ribavirin and boceprevir: analysis from the sprint-2 trial. *Hepatology* 2012 [Epub ahead of print].
 39. Sheiner PA, Schwartz ME, Mor E, *et al.* Severe or multiple rejection episodes are associated with early recurrence of hepatitis C after orthotopic liver transplantation. *Hepatology* 1995; **21**: 30–4.
 40. Machicao VI, Bonatti H, Krishna M, *et al.* Donor age affects fibrosis progression and graft survival after liver transplantation for hepatitis C. *Transplantation* 2004; **77**: 84–92.
 41. Mutimer DJ, Gunson B, Chen J, *et al.* Impact of donor age and year of transplantation on graft and patient survival following liver transplantation for hepatitis C virus. *Transplantation* 2006; **81**: 7–14.
 42. Prieto M, Berenguer M, Rayon JM, *et al.* High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: relationship with rejection episodes. *Hepatology* 1999; **29**: 250–6.
 43. Foxton MR, Quaglia A, Muiesan P, *et al.* The impact of diabetes mellitus

- on fibrosis progression in patients transplanted for hepatitis C. *Am J Transplant* 2006; **6**: 1922–9.
44. Eurich D, Boas-Knoop S, Ruehl M, et al. Relationship between the interleukin-28b gene polymorphism and the histological severity of hepatitis C virus-induced graft inflammation and the response to antiviral therapy after liver transplantation. *Liver Transpl* 2011; **17**: 289–98.
 45. Charlton MR, Thompson A, Veldt BJ, et al. Interleukin-28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection. *Hepatology* 2011; **53**: 317–24.
 46. Berenguer M, Prieto M, San JF, et al. Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients. *Hepatology* 2002; **36**: 202–10.
 47. Feray C, Samuel D, Thiers V, et al. Reinfection of liver graft by hepatitis C virus after liver transplantation. *J Clin Invest* 1992; **89**: 1361–5.
 48. Schluger LK, Sheiner PA, Thung SN, et al. Severe recurrent cholestatic hepatitis C following orthotopic liver transplantation. *Hepatology* 1996; **23**: 971–6.
 49. Fernandez I, Meneu JC, Colina F, et al. Clinical and histological efficacy of pegylated interferon and ribavirin therapy of recurrent hepatitis C after liver transplantation. *Liver Transpl* 2006; **12**: 1805–12.
 50. Berenguer M. Natural history of recurrent hepatitis C. *Liver Transpl* 2002; **8**: S14–8.
 51. Bahra M, Neumann UP, Jacob D, et al. Fibrosis progression in hepatitis C positive liver recipients after sustained virologic response to antiviral combination therapy (interferon-ribavirin therapy). *Transplantation* 2007; **83**: 351–3.
 52. Picciotto FP, Tritto G, Lanza AG, et al. Sustained virological response to antiviral therapy reduces mortality in HCV reinfection after liver transplantation. *J Hepatol* 2007; **46**: 459–65.
 53. Berenguer M, Palau A, Aguilera V, Rayon JM, Juan FS, Prieto M. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. *Am J Transplant* 2008; **8**: 679–87.
 54. Singh N, Gayowski T, Wannstedt CF, et al. Interferon-alpha for prophylaxis of recurrent viral hepatitis C in liver transplant recipients: a prospective, randomized, controlled trial. *Transplantation* 1998; **65**: 82–6.
 55. Sheiner PA, Boros P, Klion FM, et al. The efficacy of prophylactic interferon alfa-2b in preventing recurrent hepatitis C after liver transplantation. *Hepatology* 1998; **28**: 831–8.
 56. Mazzaferro V, Tagger A, Schiavo M, et al. Prevention of recurrent hepatitis C after liver transplantation with early interferon and ribavirin treatment. *Transplant Proc* 2001; **33**: 1355–7.
 57. Sugawara Y, Makuuchi M, Matsui Y, et al. Preemptive therapy for hepatitis C virus after living-donor liver transplantation. *Transplantation* 2004; **78**: 1308–11.
 58. Shergill AK, Khalili M, Straley S, et al. Applicability, tolerability and efficacy of preemptive antiviral therapy in hepatitis C-infected patients undergoing liver transplantation. *Am J Transplant* 2005; **5**: 118–24.
 59. Chalasani N, Manzarbeitia C, Ferenci P, et al. Peginterferon alfa-2a for hepatitis C after liver transplantation: two randomized, controlled trials. *Hepatology* 2005; **41**: 289–98.
 60. Angelico M, Petrolati A, Lionetti R, et al. A randomized study on Peg-interferon alfa-2a with or without ribavirin in liver transplant recipients with recurrent hepatitis C. *J Hepatol* 2007; **46**: 1009–17.
 61. Jaeckel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; **345**: 1452–7.
 62. Castells L, Vargas V, Allende H, et al. Combined treatment with pegylated interferon (alpha-2b) and ribavirin in the acute phase of hepatitis C virus recurrence after liver transplantation. *J Hepatol* 2005; **43**: 53–9.
 63. Dumortier J, Scoazec JY, Chevallier P, Boillot O. Treatment of recurrent hepatitis C after liver transplantation: a pilot study of peginterferon alfa-2b and ribavirin combination. *J Hepatol* 2004; **40**: 669–74.
 64. Oton E, Barcena R, Moreno-Planas JM, et al. Hepatitis C recurrence after liver transplantation: viral and histologic response to full-dose PEG-interferon and ribavirin. *Am J Transplant* 2006; **6**: 2348–55.
 65. Carrion JA, Navasa M, Garcia-Retortillo M, et al. Efficacy of antiviral therapy on hepatitis C recurrence after liver transplantation: a randomized controlled study. *Gastroenterology* 2007; **132**: 1746–56.
 66. Berenguer M. Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. *J Hepatol* 2008; **49**: 274–87.
 67. Xirouchakis E, Triantos C, Manousou P, et al. Pegylated-interferon and ribavirin in liver transplant candidates and recipients with HCV cirrhosis: systematic review and meta-analysis of prospective controlled studies. *J Viral Hepat* 2008; **15**: 699–709.
 68. Wang CS, Ko HH, Yoshida EM, Marra CA, Richardson K. Interferon-based combination anti-viral therapy for hepatitis C virus after liver transplantation: a review and quantitative analysis. *Am J Transplant* 2006; **6**: 1586–99.
 69. Hanouneh IA, Miller C, Aucejo F, Lopez R, Quinn MK, Zein NN. Recurrent hepatitis C after liver transplantation: on-treatment prediction of response to peginterferon/ribavirin therapy. *Liver Transpl* 2008; **14**: 53–8.
 70. Kornberg A, Kupper B, Tannapfel A, Barthel E, Thrum K, Settmacher U. Antiviral maintenance treatment with interferon and ribavirin for recurrent hepatitis C after liver transplantation: pilot study. *J Gastroenterol Hepatol* 2007; **22**: 2135–42.
 71. Walter T, Scoazec JY, Guillaud O, et al. Long-term antiviral therapy for recurrent hepatitis C after liver transplantation in nonresponders: biochemical, virological, and histological impact. *Liver Transpl* 2009; **15**: 54–63.
 72. Bzowej N, Nelson DR, Terrault NA, et al. PHOENIX: a randomized controlled trial of peginterferon alfa-2a plus ribavirin as a prophylactic treatment after liver transplantation for hepatitis C virus. *Liver Transpl* 2011; **17**: 528–38.
 73. Berenguer M, Aguilera V, Prieto M, et al. Worse recent efficacy of antiviral therapy in liver transplant recipients with recurrent hepatitis C: impact of donor age and baseline cirrhosis. *Liver Transpl* 2009; **15**: 738–46.
 74. Eurich D, Boas-Knoop S, Bahra M, et al. Role of IL28B polymorphism in the development of hepatitis C virus-induced hepatocellular carcinoma, graft fibrosis, and posttransplant antiviral therapy. *Transplantation* 2012; **93**: 644–9.
 75. Lange CM, Moradpour D, Doebering A, et al. Impact of donor and recipient IL28B rs12979860 genotypes on hepatitis C virus liver graft reinfection. *J Hepatol* 2011; **55**: 322–7.

76. Castells LL, Campos I, Bilbao I, *et al.* Cyclosporine a-based immunosuppression reduces relapse rate after antiviral therapy in transplanted patients with hepatitis C virus infection: a large multicenter cohort study. *Transplantation* 2011; **92**: 334–40.
77. Firpi RJ, Soldevila-Pico C, Morelli GG, *et al.* The use of cyclosporine for recurrent hepatitis C after liver transplant: a randomized pilot study. *Dig Dis Sci* 2010; **55**: 196–203.
78. Firpi RJ, Zhu H, Morelli G, *et al.* Cyclosporine suppresses hepatitis C virus in vitro and increases the chance of a sustained virological response after liver transplantation. *Liver Transpl* 2006; **12**: 51–7.
79. Watashi K. Alisporivir, a cyclosporin derivative that selectively inhibits cyclophilin, for the treatment of HCV infection. *Curr Opin Investig Drugs* 2010; **11**: 213–24.
80. Hirano K, Ichikawa T, Nakao K, *et al.* Differential effects of calcineurin inhibitors, tacrolimus and cyclosporin a, on interferon-induced antiviral protein in human hepatocyte cells. *Liver Transpl* 2008; **14**: 292–8.
81. Garg V, van HR, Lee JE, Alves K, Nadkarni P, Luo X. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. *Hepatology* 2011; **54**: 20–7.
82. Coilly A, Furlan V, Roche B, *et al.* Practical management of boceprevir and immunosuppressive therapy in liver transplant recipients with hepatitis C virus recurrence. *Antimicrob Agents Chemother* 2012; **56**: 5728–34.
83. Burton JR, Everson GT. Initial experience with telaprevir for treating hepatitis C virus in liver recipients: virologic response, safety and tolerability. *Am J Transplant* 2012; **12**: 188.
84. de Oliveira Pereira AP, Shin HJ, Safdar A. Post liver transplant therapy with telaprevir for recurrent hepatitis C. *Am J Transplant* 2012; **12**: 430.
85. Kwo P, Ghabril M, Lacerda M, *et al.* Use of telaprevir plus PEG interferon/ribavirin for null responders post OLT with advanced fibrosis/cholestatic hepatitis C. *J Hepatol* 2012; **56**: S86.
86. Pungpapong S, Murphy J, Henry T, *et al.* P234-III Initial experience utilising telaprevir with peginterferon and ribavirin for treatment of hepatitis C genotype 1 after liver transplantation. *Am J Transplant* 2012; **12**: 430.
87. Rogers CC, Stevens DR, Kim M, *et al.* P239-III telaprevir can be used safely with concomitant tacrolimus in the post transplant setting. *Am J Transplant* 2012; **12**: 431.
88. Sam T, Tichy E, Emre S, *et al.* P237-III pharmacokinetic effects of boceprevir co-administration of cyclosporine exposure in liver transplant recipients. *Am J Transplant* 2012; **12**: 430.
89. Schilsky M sTTEa. Boceprevir, peginterferon and ribavirin (PEGIFN/RIB) as triple antiviral therapy for recurrent hepatitis C post liver transplant: an early single center experience. *Am J Transplant* 2012; **12**: 433.
90. Sicilia M, Sandeep Mukherjee S, Fedja A, *et al.* Early experience with triple drug therapy (telaprevir, pegylated interferon a 2A and ribavirin) in patients on cyclosporine A for hepatitis C recurrence after liver transplantation. *Liver Transpl* 2012; **18**: S99.
91. Burton J, O'Leary J, Verna E, *et al.* A multicentre study of protease inhibitor-triple therapy in HCV infected liver transplant recipients: report from the CRUSH-C group. *Hepatology* 2012; **56**: No. Abstract 211; 297A.
92. An efficacy and safety study of telaprevir in patients with genotype 1 hepatitis C infection after liver transplantation (REPLACE). *Clinicaltrials.gov*: NCT01571583. Accessed November 1, 2012.
93. Fontana RJ, Hughes EA, Appelman H, Hindes R, Dimitrova D, Bifano M. Case report of successful peginterferon, ribavirin, and daclatasvir therapy for recurrent cholestatic hepatitis C after liver retransplantation. *Liver Transpl* 2012; **18**: 1053–9.
94. Fontana R, Bifano M, Hindes R, *et al.* First ever successful use of Daclatasvir and GS-7977, an Interferon-free oral regimen, in a liver transplant recipient with severe recurrent Hepatitis C. *Hepatology* 2012; **56**: No. Abstract 694, p524A. 2012.
95. Study to investigate GS-7977 and ribavirin for 24 weeks in subjects with recurrent chronic HCV post liver transplant. *Clinicaltrials.gov*: NCT01687270. Accessed December 1, 2012.
96. Giusto M, Rodriguez M, Navarro L, *et al.* Anemia is not predictive of sustained virological response in liver transplant recipients with hepatitis C virus who are treated with pegylated interferon and ribavirin. *Liver Transpl* 2011; **17**: 1318–27.
97. Ward SC, Schiano TD, Thung SN, Fiel MI. Plasma cell hepatitis in hepatitis C virus patients post-liver transplantation: case-control study showing poor outcome and predictive features in the liver explant. *Liver Transpl* 2009; **15**: 1826–33.
98. Stanca CM, Fiel MI, Kontorinis N, Agarwal K, Emre S, Schiano TD. Chronic ductopenic rejection in patients with recurrent hepatitis C virus treated with pegylated interferon alfa-2a and ribavirin. *Transplantation* 2007; **84**: 180–6.
99. Selzner N, Guindi M, Renner EL, Berenguer M. Immune-mediated complications of the graft in interferon-treated hepatitis C positive liver transplant recipients. *J Hepatol* 2011; **55**: 207–17.
100. Fiel MI, Agarwal K, Stanca C, *et al.* Posttransplant plasma cell hepatitis (de novo autoimmune hepatitis) is a variant of rejection and may lead to a negative outcome in patients with hepatitis C virus. *Liver Transpl* 2008; **14**: 861–71.
101. Levitsky J, Fiel MI, Norvell JP, *et al.* Risk for immune-mediated graft dysfunction in liver transplant recipients with recurrent HCV infection treated with pegylated interferon. *Gastroenterology* 2012; **142**: 1132–9.
102. An open-label study to explore the clinical efficacy of GS 7977 with ribavirin administered pre-transplant in preventing hepatitis C virus (HCV) recurrence post-transplant. *Clinicaltrials.gov*: NCT01559844. Accessed December 1, 2012.