Title

Telaprevir- and Boceprevir-based Triple Therapy for Hepatitis C in Liver Transplant Recipients With Advanced Recurrent Disease

Journal

Transplantation, 99(8)

ISSN

0041-1337

Authors

Verna, Elizabeth C
Saxena, Varun
Burton, James R
et al.

Publication Date

2015-08-01

DOI

10.1097/tp.0000000000000629

Peer reviewed

HHS Public Access

Author manuscript

Transplantation. Author manuscript; available in PMC 2016 April 03.

Published in final edited form as:

Transplantation. 2015 August ; 99(8): 1644–1651. doi:10.1097/TP.0000000000000629.

Telaprevir- and Boceprevir-Based Triple Therapy for Hepatitis C in Liver Transplant Recipients with Advanced Recurrent Disease: A Multicenter Study

Elizabeth C. Verna, M.D., M.S., **Varun Saxena, M.D.**, **James R. Burton Jr, M.D.**, **Jacqueline G. O'Leary, M.D.**, **Jennifer L. Dodge, M.P.H.**, **Richard T. Stravitz, M.D.**, **Joshua Levitsky, M.D.**, **James F. Trotter, M.D.**, **Gregory T. Everson, M.D.**, **Robert S. Brown Jr., M.D., M.P.H.**, and **Norah A. Terrault, M.D., M.P.H. for the CRUSH-C Consortium**

Columbia University, New York, NY (E.C.V, R.S.B); University of California, San Francisco, CA (V.S, J.L.D., N.A.T.); University of Colorado, Denver, Aurora, CO (J.R.B, G.T.E.); Baylor University Medical Center, Dallas, TX (J.G.O, J.F.T); Virginia Commonwealth University, Richmond, VA (R.T.S.); Northwestern University, Chicago, IL (J.L)

Abstract

Background—Antiviral treatment with sustained virologic response (SVR) improves survival in liver transplant (LT) recipients, and is especially relevant to patients with advanced recurrent hepatitis C virus (HCV). We assessed the safety and efficacy of protease inhibitor (PI)-based triple therapy in patients with recurrent advanced fibrosis and cholestatic hepatitis.

Methods—LT recipients with genotype 1 HCV and advanced fibrosis (F3-4/4) or cholestatic hepatitis treated with telaprevir or boceprevir-based triple therapy at 6 centers (CRUSH-C consortium) were retrospectively assessed. The primary endpoints were sustained virologic response at 12 weeks (SVR12) and safety.

Results—45 patients with advanced fibrosis and 9 with cholestatic hepatitis (74% male, 57% with genotype 1a, and 63% prior non-responders) were included. SVR12 occurred in 51% of those with advanced fibrosis and 44% with cholestatic hepatitis, and eRVR was highly predictive of SVR12. Previous null/partial response (OR 0.09, p=0.003), low platelet count (OR 1.02, p=0.004), and steroid use (OR 0.16, p=0.03) were negatively associated with SVR12 in multivariable

Corresponding Author: Norah Terrault, M.D., M.P.H., Professor of Medicine and Surgery, Director, Viral Hepatitis Center, Division of Gastroenterology, University of California San Francisco, S357, 513 Parnassus Ave., San Francisco, CA 94143-0538, Fax: 415-476-0659/Phone: 415-502-0318, Norah.Terrault@ucsf.edu.

Conflicts of Interest: Elizabeth C. Verna, M.D., M.S.: Grant support from Salix, Merck; Advisory Board for Gilead
Varun Saxena, M.D.: No conflicts
James R. Burton, Jr, M.D.: Vertex, Gilead, Abbvie
Jacqueline G. O'Leary, M.D.: Vertex, Jansen, Gilead
Jennifer L. Dodge, M.P.H.: No conflicts
Richard T. Stravitz, M.D.: Grant support from Gilead and Exalenz Biosciences
Joshua Levitsky, M.D.: Gilead Speaker's Bureau, Advisory Board for Novartis, Advisory Board and Speaker's Bureau Salix
James F. Trotter, M.D.: Gilead Speaker's Bureau
Gregory T. Everson, M.D.: Research Grants from Vertex, Merck, Abbvie, Gilead, BMS, Janssen; Advisory Board/Consultant for Abbvie, Gilead, BMS, Janssen; Equity Member/Owner HepQuant LLC
Robert S. Brown, Jr., M.D., M.P.H.: Consulting for Gilead, Abbvie, Merck and Vertex
Norah A. Terrault, M.D., M.P.H.: Grant support from Vertex, Abbvie, Gilead; Advisory/Consulting with Merck, Genetech, Gilead, BMS

models. Six (11%) patients died during or after treatment, and hepatic decompensation during treatment occurred in 22% of patients with advanced fibrosis and 33% of patients with cholestatic hepatitis. Hispanic ethnicity (OR 9.37, p=0.03) and low albumin at treatment start (OR 0.01, p=0.001) were predictive of death or decompensation in multivariable models.

Conclusions—For LT recipients with recurrent advanced HCV and at highest need of effective treatment, PI-based triple therapy achieved sustained viral clearance in ~50% of patients. However, there is significant risk of serious adverse events including hepatic decompensation, arguing for earlier therapeutic intervention. The availability of antiviral drug combinations with higher efficacy and improved safety are of particular importance for post-transplant patients with advanced disease.

INTRODUCTION

Recurrent hepatitis C virus (HCV)-related liver dysfunction remains the leading cause of graft loss and death in HCV-infected liver transplant (LT) recipients.[1, 2] HCV treatment with sustained virologic response (SVR) improves post-LT survival[3–7], and in patients with recurrent advanced fibrosis, may lead to stabilization or improvement in histology[8–15] and diminished risk of hepatic decompensation.[4, 12] Given the high rates of decompensation and death in post-LT patients with recurrent cirrhosis (up to 42% with decompensation within one year)[16, 17], and poor outcomes with retransplantation for HCV, these patients have the most to gain from effective viral eradication and disease stabilization. Unfortunately, recurrent advanced fibrosis or cirrhosis is associated with poor treatment response with peginterferon (P-IFN) and ribavirin dual therapy.[3, 10, 13, 18–20] Furthermore, data are limited on the treatment of patients with cholestatic HCV, a severe form of recurrent disease associated with high mortality when untreated.[19, 21–24]

Direct-acting antiviral agents, including NS3/4A protease inhibitors, NS5B polymerase inhibitors and NS5A inhibitors are a major advance in HCV therapeutics. When used in combination with P-IFN and ribavirin, the protease inhibitors (PIs), telaprevir and boceprevir, increased rates of SVR in treatment naïve[25–29] and treatment experienced[30–32] immunocompetent patients with genotype 1 HCV. These triple therapy regimens are also effective in patients with advanced fibrosis and cirrhosis in the non-transplant setting, though with somewhat diminished response rates and more significant toxicities. [33–35] Up until late 2013, PI-triple therapy with telaprevir or boceprevir was regarded as the best treatment option patients with genotype 1 HCV disease, including LT recipients. The risk of graft loss especially in patients advanced fibrosis or cholestatic hepatitis led many centers to use protease inhibitor-based regimens in LT recipients even in the face of concerns regarding significant medication interactions between the PIs and standard immunosuppressive agents (most prominently calcineurin inhibitors[36, 37] and mammalian target of rapamycin inhibitors[38]), as well as worsening of the kidney dysfunction and cytopenias often present post-LT. In this study, we focus on the efficacy and safety of triple antiviral therapy in LT recipients with advanced fibrosis and cholestatic hepatitis and identify key factors associated with a successful outcome.

In many countries, PI-triple therapy with telaprevir and boceprevir has been only recently approved and will remain the mainstay of treatment in the near future. While those with less advanced disease may be able to await newer treatment options, including P-IFN free regimens, LT patients with advanced fibrosis may need to be considered for PI triple therapy. Thus, our detailed experience in patients with advanced fibrosis is particularly relevant even as HCV treatment evolves.

MATERIALS AND METHODS

Patients

This is a retrospective multicenter cohort study of adult liver transplant recipients with recurrent advanced disease treated with either telaprevir or boceprevir-based triple therapy in the Consortium to Study Health Outcomes in HCV Liver Recipients (CRUSH-C), a group of six liver transplant centers in the United States. The overall study results have been previously published.[39] For the current study, all patients with genotype 1 HCV RNA detectable infection and advanced fibrosis defined by evidence of chronic hepatitis on liver biopsy with either Metavir or Scheur fibrosis stages 3–4, or cholestatic hepatitis were included. Cholestatic hepatitis was diagnosed based upon the hepatologist's assessment with consideration of standard biochemical and histologic criteria[40, 41]. Biopsies were not centrally reread for the purposes of this study. This study was approved by the institutional review board at each center.

Treatment Regimen

The majority of patients in the cohort (94%) were treated with a lead-in of P-IFN and ribavirin prior to initiation of telaprevir or boceprevir. The target P-IFN dose was peginterferon alfa-2a 180 mcg weekly, peginterferon alfa-2b 1.5 mcg/kg weekly, or consensus interferon 12 mcg/kg daily, while the target ribavirin dose was weight-based (adjusted for renal function). Thirteen percent of patients were treated with a prolonged (≥90 day) lead-in; 9% of patients with advanced fibrosis and 33% of those with cholestatic hepatitis. These were generally patients with virologic non-response to P-IFN and ribavirin dual therapy that remained on treatment for disease stabilization while awaiting availability of new agents.

The choice of telaprevir (750mg three times daily or 1125mg twice daily for 12 weeks) or boceprevir (800mg three times daily for 44 weeks) in combination with P-IFN and ribavirin was at the discretion of the investigator. Stopping rules included discontinuation of the PI in the setting of virologic failure or a significant adverse event. Virologic failure for those receiving telaprevir was defined as a viral load of >1000 IU/mL 4 to 12 weeks after starting telaprevir or detectable HCV RNA at 24 weeks. For those receiving boceprevir, virologic failure was defined as HCV RNA >100 IU/mL after week 4 of boceprevir and detectable HCV RNA at week 28.

In general, erythropoietin and transfusion were used to maintain hemoglobin levels >10 g/dL, granulocyte colony stimulating factor (GCSF) was used to keep absolute neutrophil counts >1000 per mm^3 and eltrombopag to manage severe thrombocytopenia (<30K per

mm^3). The choice of immunosuppression was also at the discretion of investigator. All patients had a steady state of immunosuppression before antiviral therapy was started, then the calcineurin inhibitor or mammalian target of rapamycin inhibitor was dose reduced throughout the duration of PI therapy. Pre- and post-treatment calcineurin inhibitor doses were recorded in addition to the use of mTOR inhibitors, mycophenolate mofetil and steroids. Antibacterial prophylaxis was considered if patients had clinically evident recurrent portal hypertension.

Outcomes

The primary endpoint was 12 week sustained virologic response (SVR12), defined as the proportion of patients with undetectable plasma HCV RNA 12 weeks after treatment completion. Secondary endpoints included rates of rapid virologic response (RVR), defined as undetectable HCV RNA 4 weeks after PI initiation, and extended rapid virologic response (eRVR), defined as undetectable HCV RNA 4 and 12 weeks after PI initiation. Additional virologic outcomes assessed include end of treatment response (EOTR), defined as undetectable HCV RNA at end of therapy, relapse, defined as post-treatment recurrence of detectable HCV RNA during the 12 week follow up period, and breakthrough, defined as emergence of detectable HCV RNA after being undetectable or >1 log increase in HCV RNA above nadir HCV RNA during treatment. Missing HCV RNA values were considered to be positive.

HCV RNA levels were measured prior to treatment initiation and prior to protease inhibitor initiation, at weeks 4, 12, and 24 weeks after starting the PI, at the end of treatment and 4 and 12 weeks after treatment discontinuation. Plasma HCV RNA levels were quantified by COBAS TaqMan HCV RNA assay, version 2.0 (Roche) with lower limit of detection of 43 or 18 IU per mL at five of the six centers. One center (17% of total cohort) used a semi-automated real time polymerase chain reaction assay (Abbott) with lower limit of detection of 12 IU per mL.

Safety

All serious adverse events including mortality and the need for hospitalization were recorded. In addition, evidence of hepatic decompensation (defined as the development of ascites, encephalopathy or portal hypertensive bleeding), allograft rejection, kidney dysfunction and anemia requiring transfusion were noted. Laboratory assessment including blood counts and basic chemistries were collected at baseline, at the start of the PI, weeks 2–4, week 8, 12, 16, end of therapy and 12 weeks after cessation of therapy. In addition, the use of growth factors (erythropoietin, GCSF and eltrombopag) was assessed along with the incidence of dose reductions and early discontinuations of P-IFN, ribavirin and the PI.

Statistical Analysis

The proportion of patients achieving SVR12 and secondary virologic outcomes are compared between patients with advanced fibrosis and cholestatic hepatitis. Dichotomous variables are described with frequencies (percent) and continuous variables as medians with range or interquartile range. Groups were compared using Fisher’s exact or Wilcoxon rank sum tests, as appropriate and a p-value less than 0.05 was considered significant. Logistic

regression was performed to assess predictors of SVR12 among patients with advanced fibrosis. Backwards elimination technique was utilized, initially including all predictors with significance of $p<0.2$ with sequential elimination of non-significant variables. All analyses were completed using SAS version 9.2 (Cary, NC).

RESULTS

Patient Characteristics

A total of 54 patients were included in the analysis, 45 (83%) with advanced fibrosis and 9 (17%) with cholestatic hepatitis. The median (IQR) age was 58 (55–61) years at the start of treatment, 74% were male, and 65% were Caucasian (Table 1). The majority of patients had unfavorable treatment characteristics, including a predominance of HCV genotype 1a (58%), IL28B non-CC genotype (67%), and previous post-transplant treatment failure with P-IFN and ribavirin dual therapy (63%). Despite advanced fibrosis, these patients were generally well compensated at the start of treatment with a median (IQR) MELD of 10 (8–14), and 87% Childs-Turcotte–Pugh (CTP) class A. The median (IQR) time from transplant to initiation of treatment was 4.3 (2.5–8.9) years. Baseline characteristics were generally similar between patients with advanced fibrosis and cholestatic hepatitis (Table 1). Patients with cholestatic hepatitis were older (median age 62 v. 57 years, p=0.05), more recently transplanted (median 1.5 v. 4.6 years post-LT, p=0.009), and were more likely to be African American (33% v. 7%, p=0.05), treatment naïve (78% v. 29%, p=0.009) and CTP class C at treatment initiation (22% v. 0%, p=0.02).

Antiviral Regimen

All patients were treated with a combination of a PI (telaprevir in 91% or boceprevir in 9%), P-IFN (alfa 2a in 93%) and ribavirin (Table 2). There were no significant differences in choice of antiviral treatment agents or duration of lead-in between the advanced fibrosis and cholestatic hepatitis groups. The median initial, minimum and maximum doses of P-IFN and ribavirin were similar between groups. The median (IQR) total treatment duration for the cohort was 47 (26–51) weeks. Patients with cholestatic hepatitis had a significantly shorter median total duration of treatment from the time of PI initiation compared to those with advanced fibrosis (21 v. 43 weeks, p=0.04), due to early treatment discontinuation.

Immunosuppression

Eighty-four (87%) patients were on calcineurin inhibitors (20% tacrolimus and 67% cyclosporine) at the start of antiviral therapy, and 7 (13%) on mTOR inhibitors. In addition, 76% were on mycophenolate mofetil or mycophenolic acid and 24% were on maintenance prednisone. Patients with cholestatic hepatitis were more likely to be on tacrolimus as their CNI (67% v. 11%, p=0.001), and had a trend towards a higher frequency of steroid use (44% v. 20%, p=0.19) than those with advanced fibrosis.

All patients had a reduction in CNI dosing at the start of the PI (Table 2). The median percent reduction in CNI dose was similar between groups [70% (IQR 62–80) and 79% (IQR 70–89)] for advanced fibrosis and cholestatic hepatitis, respectively; p=0.17).

Treatment Response

Treatment response data are summarized in Figure 1. SVR12 rates were statistically similar in patients with advanced fibrosis (51%, 95% CI: 36–66%) and cholestatic hepatitis (44%, 95% CI: 14–79%), p=1.00. Rates of RVR, eRVR, and EOTR were also similar between groups. Four (13%) of patients experienced relapse in the 12 weeks following treatment discontinuation, and relapse rates were similar between groups.

Predictors of Treatment Response

On treatment responses were also highly predictive of SVR12 including >1 log drop in viral load in the lead-in phase of treatment (5.25, p=0.007) and eRVR (55.0, p<0.001). Rapid treatment response was the strongest predictor of SVR12 (Figure 2). For patients who achieved eRVR, 83% went on to achieve SVR12 compared to only 8% of those without eRVR (p<0.001). The overall positive (PPV) and negative predictive (NPV) values of eRVR to predict SVR12 were 83% and 92%, respectively.

Baseline predictors of SVR12 among these 54 patients with advanced disease were also assessed, with Hispanic ethnicity (OR 0.16, p=0.03), previous null/partial response (0.24, p=0.02), IL28B genotype CC (7.0, P=0.02), baseline albumin per mg/dL (3.87, p=0.03), baseline platelets per 1K (1.01, p=0.02) and steroid use (0.21, p=0.03) significant predictors in univariate analysis (Table 3). In the final multivariable model of pre-treatment characteristics, previous nonresponse (OR 0.09, p=0.003), platelets per 1K (1.02, p=0.004), and steroid use (0.16, p=0.03) remained significantly predictive.

Safety

Adverse events and safety data are summarized in Table 4. The frequency of use of erythropoietin and transfusions for management of anemia were high and similar between patients with advanced fibrosis and cholestatic hepatitis. Dose reductions of ribavirin and P-IFN were common and of similar frequency between groups, though early treatment discontinuation due to adverse events was more common in the cholestatic patients (56% v. 16%, p=0.02).

Progression of liver disease including hepatic decompensation at any time on treatment occurred in 24% and progression from CTP class A to B/C while on treatment occurred in 28% overall, including 31% of advanced disease patients and 11% of those with cholestatic hepatitis (p=0.42). Six (11%) patients died, 5 (11%) with advanced fibrosis and 1 (11%) of those with cholestatic hepatitis. All deaths were attributed to progressive complications of liver failure.

Univariate predictors of death or decompensation in the cohort included Hispanic ethnicity (OR 6.17, p=0.01), albumin per g/dL at the start of therapy (0.02, p=0.001), and the presence of encephalopathy (12.0, p=0.04). In multivariable analysis, Hispanic ethnicity (OR9.37, p=0.03) and albumin per g/dL (0.01, p=0.001) remained predictive.

DISCUSSION

Patients with recurrent advanced liver disease post-LT have the most urgent need for effective antiviral therapy. We report the safety and efficacy of PI-based triple therapy in this difficult-to-treat patient group. SVR12 was achieved in 51% of patients with F3-F4 recurrent fibrosis, which is encouraging given the multiple negative prognostic factors present in many of these patients. This represents a significant advance from P-IFN and ribavirin dual therapy.

Early on treatment response (eRVR) was highly predictive of SVR12 in the cohort. This correlation was particularly pronounced in the advanced disease group with a NPV of 95% for those who did not achieve eRVR. We would therefore advocate that the failure to achieve eRVR be considered a stopping rule in patients with advanced disease, as the benefits of continuing treatment in these patients is likely outweighed by the considerable risks. This may be a particularly useful clinical predictor to consider when toxicities are encountered early in treatment. As in non-transplant patients with advanced disease, other significant predictors of SVR among this cohort included previous treatment experience, as baseline laboratory parameters indicative of more advanced cirrhosis and portal hypertension, such as albumin and platelets.[33]

Immunosuppressive regimens including the proportion of patients on dual immunosuppression and baseline CNI dosing were similar between groups. The choice of baseline CNI was not significantly predictive of SVR12 in this small study, and it remains uncertain whether switching CNI from tacrolimus to cyclosporine is warranted. However, chronic steroid use at the time of treatment initiation was significantly predictive of treatment failure in multivariable modeling. Thus, minimization of steroid use prior to HCV treatment should be considered.

This is also the first report of SVR12 rates in patients with cholestatic HCV treated with PI-based triple therapy. While these patients represent a small percentage of post-LT patients with recurrence, their treatment urgency and complexity are the greatest. In the few small series of cholestatic HCV patients treated with P-IFN and ribavirin, SVR rates range from 0–30%.[21–24, 40, 42] PI-based triple therapy improved this significantly to 44% (95% CI 14–79%) SVR12, though overall response rates in this group remain poor, perhaps due to poor tolerability in this group. There are now case reports of successful treatment of these patients using the NS5A replication complex inhibitor daclatasvir either in combination with P-IFN and ribavirin[43], or with the polymerase inhibitor sofosbuvir.[44] It is likely the future all oral regimens, with improved side effect profiles, will significantly improve treatment outcomes in these patients.

Adverse events were common in our cohort, including anemia requiring transfusion, kidney dysfunction, hospitalization and death. In addition, progressive hepatic decompensation was common, with 28% of the cohort advancing from CTP class A to B on the P-IFN and ribavirin lead-in and 22% and 33% experiencing clinical decompensation on treatment in the advanced fibrosis and cholestatic hepatitis groups, respectively. Predictors of clinical decompensation and death in our cohort included markers of more severe disease at

treatment inititiation including the presence of hepatic encephalopathy at baseline and low albumin. Unexpectedly, Hispanic ethnicity was associated with decompensation/death. The reason for this association is unclear, and given the small number of Hispanic patients (n=11) in the cohort, this finding needs to be confirmed in larger studies.

With the recent approval of new direct acting antiviral agents, sofosbuvir and simeprevir, safe and effective interferon-free regimens are available in some countries. However, these medicines have not been extensively studied in LT recipients, and may have limited applicability in patients with significant renal (sofosbuvir) or hepatic (simeprevir) impairment. In a preliminary report of a phase 2 open-label study of LT recipients who received sofosbuvir and ribavirin for 24 weeks, 100% of patients achieved RVR and EOTR, however 77% achieved SVR4, with SVR12 rates yet to be reported.[45] While these results are promising, this study included patients with genotypes 2–4, only 66% had advanced recurrent disease (Metavir stage 3–4) and no patients had evidence of hepatic decompensation, rendering this population somewhat easier to treat. A more comparable population to the advanced disease population reported here, is that treated via the sofosbuvir compassionate use program.[46] Of the 44 patients (19 had cholestatic hepatitis) treated for up to 48 weeks, 71% experienced clinical improvement, and the SVR12 rate was 60% among 20 patients who completed treatment. These results suggest that LT patient with advanced disease including those with cholestatic hepatitis remain in high need of more efficacious therapies.

This study has some methodological limitations due to its retrospective design. The liver histology was not centrally reviewed and therefore we cannot exclude the possibility of misclassification, especially in the cholestatic hepatitis patients where the diagnostic criteria are less standardized.[23, 40, 41, 47] This misclassification is unlikely as all CRUSH-C centers are large academic transplant centers with experienced pathologists. The immunosuppression regimen also varied between patients and centers perhaps leading to additional heterogeneity, but this enhances the study’s generalizability. Finally, follow up for these patients was generally limited to SVR12 and serial biopsy data are not available. Thus, the long-term benefits of SVR such as histological stabilization or regression of fibrosis, prevention of hepatic decompensation and improved survival cannot be evaluated.

In summary, substantially higher SVR12 rates are achieved with PI-based triple anti-HCV therapy in LT recipients with recurrent advanced disease than previously reported for dual therapy. Although these patients may benefit the most from viral clearance, treatment should be undertaken with care given the risk of hepatic decompensation on therapy. Moreover, to maximize benefits and minimize risk, stopping treatment in those who fail to achieve eRVR is recommended. While HCV treatment is likely to rapidly evolve in the coming years with a focus on IFN-free regimens, these new agents including sofosbuvir may not be widely available worldwide for some time, and given the high risk of decompensation and death in LT recipients with recurrent advanced disease, many patients will be unable to wait. Telaprevir- or boceprevir- based triple therapy therefore may remain a reasonable approach in selected patients and scenarios. Clinical trials with new antiviral combinations, including IFN-and ribavirin-free regimens are urgently needed in this population with the goal of providing safer and more effective treatment before the development of advanced fibrosis.

Acknowledgments

Funding: This project was supported in part by the Biostatistics Core of the UCSF Liver Center (P30 DK026743).

Abbreviations

CNI	calcineurin inhibitor
CTP	Childs-Turcotte–Pugh
EOTR	end of treatment response
eRVR	extended rapid virologic response
GCSF	granulocyte colony stimulating factor
HCV	Hepatitis C virus
LT	liver transplantation
NPV	negative predictive value
P-IFN	pegylated interferon
PPV	positive predictive value
PI	protease inhibitor
RVR	rapid virologic response
SVR	sustained virologic response

References

1. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999–2008. Am J Transplant. 2010; 10:1003–1019. [PubMed: 20420649]
2. Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. Gastroenterology. 2002; 122:889–896. [PubMed: 11910340]
3. Picciotto FP, Tritto G, Lanza AG, Addario L, De Luca M, Di Costanzo GG, et al. Sustained virological response to antiviral therapy reduces mortality in HCV reinfection after liver transplantation. J Hepatol. 2007; 46:459–465. [PubMed: 17196700]
4. 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; 8:679–687. [PubMed: 18294165]
5. Bizollon TPP, Mabrut JY, Chevallier M, Adham M, Radenne S, Souquet JC, Ducerf C, Baulieux J, Zoulin F, Trepo C. Benefit of sustained virological response to combination therapy on graft survival of liver transplanted patients with recurrent chronic hepatitis C. Am J Transplant. 2005; 5:1909–1913. [PubMed: 15996238]
6. Veldt BJ, Poterucha JJ, Watt KD, Wiesner RH, Hay JE, Kremers WK, et al. Impact of pegylated interferon and ribavirin treatment on graft survival in liver transplant patients with recurrent hepatitis C infection. Am J Transplant. 2008; 8:2426–2433. [PubMed: 18727694]
7. Crespo G, Carrion JA, Coto-Llerena M, Marino Z, Lens S, Perez-Del-Pulgar S, et al. Combinations of simple baseline variables accurately predict sustained virological response in patients with recurrent hepatitis C after liver transplantation. J Gastroenterol. 2012
8. Xirouchakis E, Triantos C, Manousou P, Sigalas A, Calvaruso V, Corbani A, 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. [PubMed: 18673428]

9. Angelico M, Petrolati A, Lionetti R, Lenci I, Burra P, Donato MF, 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; 46:1009–1017. [PubMed: 17328985]
10. Carrion JA, Navasa M, Garcia-Retortillo M, Garcia-Pagan JC, Crespo G, Bruguera M, et al. Efficacy of antiviral therapy on hepatitis C recurrence after liver transplantation: a randomized controlled study. Gastroenterology. 2007; 132:1746–1756. [PubMed: 17484872]
11. 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; 14:53–58. [PubMed: 18161839]
12. Berenguer M, Schuppan D. Progression of liver fibrosis in post-transplant hepatitis C: mechanisms, assessment and treatment. J Hepatol. 2013; 58:1028–1041. [PubMed: 23262248]
13. Roche B, Sebagh M, Canfora ML, Antonini T, Roque-Afonso AM, Delvart V, et al. Hepatitis C virus therapy in liver transplant recipients: response predictors, effect on fibrosis progression, and importance of the initial stage of fibrosis. Liver Transpl. 2008; 14:1766–1777. [PubMed: 19025933]
14. Berenguer M, Aguilera V, Rubin A, Ortiz C, Jimenez M, Prieto M. Comparison of two non-contemporaneous HCV-liver transplant cohorts: strategies to improve the efficacy of antiviral therapy. J Hepatol. 2012; 56:1310–1316. [PubMed: 22314429]
15. Oton E, Barcena R, Moreno-Planas JM, Cuervas-Mons V, Moreno-Zamora A, Barrios C, et al. Hepatitis C recurrence after liver transplantation: Viral and histologic response to full-dose PEG-interferon and ribavirin. Am J Transplant. 2006; 6:2348–2355. [PubMed: 16869810]
16. Berenguer M, Prieto M, Rayon JM, Mora J, Pastor M, Ortiz V, et al. Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. Hepatology. 2000; 32:852–858. [PubMed: 11003634]
17. Samuel D, Forns X, Berenguer M, Trautwein C, Burroughs A, Rizzetto M, et al. Report of the monothematic EASL conference on liver transplantation for viral hepatitis (Paris, France, January 12–14, 2006). J Hepatol. 2006; 45:127–143. [PubMed: 16723165]
18. Berenguer M, Aguilera V, Prieto M, Ortiz C, Rodriguez M, Gentili F, 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; 15:738–746. [PubMed: 19562707]
19. Berenguer M. Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. J Hepatol. 2008; 49:274–287. [PubMed: 18571272]
20. Ponziani FR, Annicchiarico EB, Siciliano M, D'Aversa F, Pompili M, Gasbarrini A. Treatment of hepatitis C in compensated cirrhotic patients is equally effective before and after liver transplantation. World J Gastroenterol. 2013; 19:3255–3262. [PubMed: 23745027]
21. Ong JP, Younossi ZM, Gramlich T, Goodman Z, Mayes J, Sarbah S, et al. Interferon alpha 2B and ribavirin in severe recurrent cholestatic hepatitis C. Transplantation. 2001; 71:1486–1487. [PubMed: 11391241]
22. Gopal DV, Rosen HR. Duration of antiviral therapy for cholestatic HCV recurrence may need to be indefinite. Liver Transpl. 2003; 9:348–353. [PubMed: 12682884]
23. Satapathy SK, Sclair S, Fiel MI, Del Rio Martin J, Schiano T. Clinical characterization of patients developing histologically-proven fibrosing cholestatic hepatitis C post-liver transplantation. Hepatol Res. 2011; 41:328–339. [PubMed: 21426450]
24. Duarte-Rojo A, Budhraja V, Veldt BJ, Goldstein DD, Watt KD, Heimbach JK, et al. Interleukin-28B and fibrosing cholestatic hepatitis in posttransplant hepatitis C: A case-control study and literature review. Liver Transpl. 2013; 19:1311–1317. [PubMed: 24039107]
25. McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med. 2009; 360:1827–1838. [PubMed: 19403902]

26. Hezode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med. 2009; 360:1839–1850. [PubMed: 19403903]
27. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011; 364:2405–2416. [PubMed: 21696307]
28. Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet. 376:705–716. [PubMed: 20692693]
29. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364:1195–1206. [PubMed: 21449783]
30. McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med. 2010; 362:1292–1303. [PubMed: 20375406]
31. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011; 364:2417–2428. [PubMed: 21696308]
32. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364:1207–1217. [PubMed: 21449784]
33. Hezode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. J Hepatol. 2013
34. Colombo M, Fernandez I, Abdurakhmanov D, Ferreira PA, Strasser SI, Urbanek P, et al. Safety and on-treatment efficacy of telaprevir: the early access programme for patients with advanced hepatitis C. Gut. 2013
35. Ogawa E, Furusyo N, Nakamuta M, Kajiwara E, Nomura H, Dohmen K, et al. Telaprevir-based triple therapy for chronic hepatitis C patients with advanced fibrosis: a prospective clinical study. Aliment Pharmacol Ther. 2013; 38:1076–1085. [PubMed: 24099469]
36. Garg V, van Heeswijk R, Lee JE, Alves K, Nadkarni P, Luo X. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. Hepatology. 2011; 54:20–27. [PubMed: 21618566]
37. Hulskotte E, Gupta S, Xuan F, van Zutven M, O'Mara E, Feng HP, et al. Pharmacokinetic interaction between the hepatitis C virus protease inhibitor boceprevir and cyclosporine and tacrolimus in healthy volunteers. Hepatology. 2012; 56:1622–1630. [PubMed: 22576324]
38. O'Leary JG, McKenna GJ, Klintmalm GB, Davis GL. Effect of telaprevir on the pharmacokinetics of sirolimus in liver transplant recipients. Liver Transpl. 2013; 19:463–465. [PubMed: 23408534]
39. Burton JR, O'Leary JG, Verna EC, Saxena V, Dodge JL, Stravitz RT, et al. A US Multicenter Study of Hepatitis C Treatment of Liver Transplant Recipients with Protease-Inhibitor Triple Therapy. J Hepatol. 2014 In Press.
40. Verna EC, Abdelmessih R, Salomao MA, Lefkowitch J, Moreira RK, Brown RS Jr. Cholestatic hepatitis C following liver transplantation: an outcome-based histological definition, clinical predictors, and prognosis. Liver Transpl. 2013; 19:78–88. [PubMed: 23081888]
41. 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. [PubMed: 14586888]
42. Fernandez I, Meneu JC, Colina F, Garcia I, Munoz R, Castellano G, et al. Clinical and histological efficacy of pegylated interferon and ribavirin therapy of recurrent hepatitis C after liver transplantation. Liver Transpl. 2006; 12:1805–1812. [PubMed: 17133585]
43. 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; 18:1053–1059. [PubMed: 22706796]

44. Fontana RJ, Hughes EA, Bifano M, Appelman H, Dimitrova D, Hindes R, et al. Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C. Am J Transplant. 2013; 13:1601–1605. [PubMed: 23593993]

45. Samuel D, Charlton M, Gane E, Brown R, Curry M, Kwo P, et al. Sofosbuvir and Ribavirin for the Treatment of Recurrent Hepatitis C Infection After Liver Transplantation: Results of a Prospective, Multicenter Study. J Hepatol. 2014; 60:S499.

46. Forns X, Prieto M, Charlton M, McHutchison JG, Symonds WT, Denning J, et al. Sofosbuvir Compassionate Use Progran for Patients wtih Severe Recurrent Hepatitis C Including Fibrosing Cholestatic Hepatitis Following Liver Transplantation. J Hepatol. 2014; 60:S26.

47. Narang TK, Ahrens W, Russo MW. Post-liver transplant cholestatic hepatitis C: a systematic review of clinical and pathological findings and application of consensus criteria. Liver Transpl. 2010; 16:1228–1235. [PubMed: 21031537]

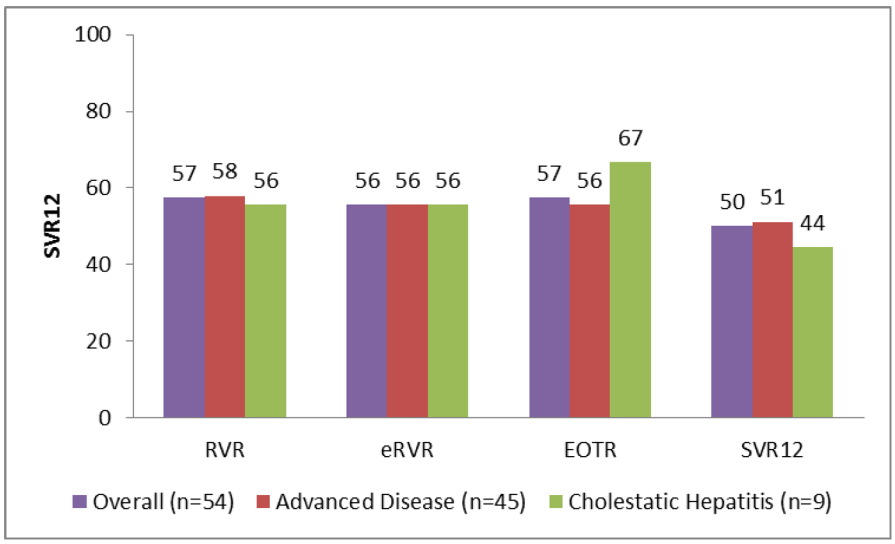

Figure 1.
Treatment response by advanced disease category.

Table 1

Patient baseline characteristics at the start of treatment.

Characteristic	Total Cohort (n = 54)	Advanced Fibrosis (n = 45)	Cholestatic Hepatitis (n = 9)	p-value
Age, years, median (IQR)	58 (55–61)	57 (55–60)	62 (57–63)	0.05
Male (%)	40 (74)	33 (73)	7 (78)	1.00
Race/Ethnicity (%)				
Caucasian	35 (65)	32 (71)	3 (33)	0.05
African American	6 (11)	3 (7)	3 (33)	0.05
Hispanic	11 (20)	9 (20)	2 (22)	1.00
Asian	2 (4)	1 (2)	1 (11)	0.31
Genotype 1a (vs. 1b or unknown)	31 (57)	26 (58)	5 (56)	1.00
Previous post-LT treatment (%)				
Null/partial response	23 (43)	22 (49)	1 (11)	0.06
Relapse	11 (20)	10 (22)	1 (11)	0.67
No previous treatment	20 (37)	13 (29)	7 (78)	0.009
IL28B CC (vs. CT/TT)[^] (%)	10 (33)	7 (32)	3 (38)	1.00
Pretreatment viral load, log international units/mL, median (IQR)[*]	6.6 (6.0–7.0)	6.6 (5.9–7.0)	6.7 (6.0–7.3)	0.44
Fibrosis stage (%)				
1	1 (2)	0 (0)	1 (11)	NA
2	6 (11)	0 (0)	6 (67)	
3	29 (54)	27 (60)	2 (22)	
4	18 (33)	18 (40)	0 (0)	
Laboratory values, median (IQR)				
Bilirubin start tx, mg/dL	1.4 (0.8–1.7)	1.2 (0.8–1.7)	1.8 (1.4–13.3)	0.007
eGFR start tx, mL/min/m^2	61.6 (53.8–74.5)	61.0 (54.9–69.5)	73.0 (46.3–75.5)	0.58
INR[#]	1.1 (1.0–1.2)	1.1 (1.1–1.2)	1.0 (0.9–1.1)	0.08
Albumin mg/dL	3.6 (3.3–4.0)	3.6 (3.4–4.0)	3.5 (3.2–4.3)	0.91
Platelets	120 (87–169)	119 (87–163)	158 (90–172)	0.65
Laboratory MELD[¥]	10 (8–14)	9 (8–14)	11 (9–17)	0.17
Ascites (%)				
None	50 (93)	43 (96)	7 (78)	0.12
Medically controlled	3 (6)	2 (4)	1 (11)	0.43
Medically not-controlled	1 (2)	0 (0)	1 (11)	0.17
Hepatic encephalopathy (%)				

Characteristic	Total Cohort (n = 54)	Advanced Fibrosis (n = 45)	Cholestatic Hepatitis (n = 9)	p-value
None	50 (93)	43 (96)	7 (78)	0.12
Medically controlled	4 (7)	2 (4)	2 (22)	
CTP Class (%)				
A	47 (87)	42 (93)	5 (56)	0.01
B	5 (9)	3 (7)	2 (22)	0.19
C	2 (4)	0 (0)	2 (22)	0.02
Weeks from last biopsy to treatment, median (IQR)	26 (11–94)	30 (12–101)	8 (6–11)	0.003
Years from LT to treatment, median (IQR)	4.3 (2.5–8.9)	4.6 (2.9–8.9)	1.5 (1.1–3.4)	0.009

^ A total of 30 patients had IL28B genotype data available.

* Pretreatment viral load available in 53 patients.

INR at the start of treatment available in 38 patients.

¥ MELD was available in 38 patients.

Table 2

Antiviral and immunosuppression treatment regimens by disease status.

Characteristic	Total Cohort (n = 54)	Advanced Fibrosis (n = 45)	Cholestatic Hepatitis (n = 9)	p-value
Protease Inhibitor (%)				
Telaprevir	49 (91)	42 (93)	7 (78)	0.19
Boceprevir	5 (9)	3 (7)	2 (22)	
P-IFN (%)				
2a	50 (93)	41 (91)	9 (100)	1.00
2b/other	4 (7)	4 (9)	0 (0)	
Lead-in (%)	51 (94)	43 (96)	8 (89)	0.43
Lead-in, median (IQR) days	32 (28–62)	30 (28–56)	54 (33–126)	0.19
Extended lead-in (≥ 90 days)	7 (13)	4 (9)	3 (33)	0.08
Total time on treatment, weeks, median (IQR)	47 (26–51)	48 (30–51)	32 (24–44)	0.15
Weeks of treatment from PI, median (IQR)	42 (14–45)	43 (22–46)	21 (2–43)	0.04
Baseline CNI (%)				
Tacrolimus	11 (20)	5 (11)	6 (67)	0.001
Cyclosporine	36 (67)	34 (76)	2 (22)	0.004
Other	7 (13)	6 (13)	1 (11)	1.00
Median (IQR) average daily dose pre-PI				
Tacrolimus	1 (1–3)	1 (1–3)	1.5 (0.5–2)	0.51
Cyclosporine	200 (112–200)	200 (100–200)	350 (300–400)	0.02
Median (IQR) average daily dose on PI				
Tacrolimus	0.1 (0.04–0.5)	0.04 (0.02–0.27)	0.31 (0.07–0.5)	0.05
Cyclosporine	50 (37.5–61.4)	50 (37.5–60.4)	75 (50–100)	0.14
Median (IQR) percent CNI dose reduction on PI				
Tacrolimus	87 (75–96)	96 (90–98)	79 (74–90)	0.09
Cyclosporine	68 (62–76)	69 (61–78)	77 (67–88)	0.92
Mycophenylate mofetil or mycophenolic acid (%)	41 (76)	35 (78)	6 (67)	0.67
Steroids (%)	13 (24)	9 (20)	4 (44)	0.19

Table 3

Predictors of SVR12 among patients with advanced recurrent HCV

Covariate	Univariate		Multivariate	
	Odd Ratio (95% Confidence Interval)	P-value	Odd Ratio (95% Confidence Interval)	P-value
Age per year	1.01 (0.93–1.10)	0.75		
Male gender	2.20 (0.62–7.74)	0.22		
Hispanic ethnicity	0.16 (0.03–0.83)	0.03		
African American race	0.46 (0.08–2.75)	0.40		
Genotype 1a (vs. 1b or unknown)	0.46 (0.16–1.40)	0.17		
Previous null/partial response (vs. relapse and no previous therapy)	0.24 (0.08–0.76)	0.02	0.09 (0.02–0.45)	0.003
IL28B genotype CC (vs. CT/TT)*	7.00 (1.29–37.91)	0.02		
Bilirubin, mg/dL,	0.80 (0.58–1.10)	0.17		
eGFR, mL/min/m^2	0.98 (0.95–1.01)	0.12		
Albumin, mg/dL	3.87 (1.17–12.84)	0.03		
Platelets per 1,000/mm^3	1.01 (1.00–1.02)	0.02	1.02 (1.01–1.04)	0.004
Ascites	0.31 (0.03–3.16)	0.32		
Hepatic encephalopathy	1.00 (0.12–7.67)	1.00		
Telaprevir (vs. Boceprevir)	0.22 (0.02–2.12)	0.19		
Baseline CNI		0.14		
Tacrolimus	0.51 (0.13–2.06)	0.34		
Cyclosporine	ref			
Other	1.19 (0.23–6.11)	0.83		
Mycophenylate mofetil or mycophenolic acid	0.54 (0.15–1.93)	0.34		
Steroids	0.21 (0.05–0.89)	0.03	0.16 (0.03–0.84)	0.03
Baseline VL, log international units/mL	1.41 (0.75–2.66)	0.28		

Table 4

Safety and adverse events by disease category.

Safety Outcome	Total Cohort (n = 54)	Advanced Fibrosis (n = 45)	Cholestatic Hepatitis (n = 9)	p-value
Ribavirin dose reduction (%)	45 (83)	38 (84)	7 (78)	0.64
Peg-IFN dose reduction (%)	21 (39)	16 (36)	5 (56)	0.29
Tx discontinuation[^]				
Due to adverse event	12 (22)	7 (16)	5 (56)	0.02
Due to virologic failure	15 (28)	14 (31)	1 (11)	0.42
Growth factor use (%)				
Erythropoetin	41 (76)	33 (73)	8 (89)	0.43
Filgrastim	25 (46)	21 (47)	4 (44)	1.00
Elthrombopag	3 (6)	2 (4)	1 (11)	0.43
Anemia (Hemoglobin < 8 mg/dl)[#] (%)	14 (26)	12 (27)	2 (25)	1.00
Required transfusion(s) (%)	30 (56)	24 (53)	6 (67)	0.72
Maximum change in eGFR, median (IQR)	41.3 (30.5–51.2)	41.5 (30.4–50.5)	38.8 (32.8–53.2)	0.69
Creatinine increase of ≥0.5 mg/dL (%)	20 (37)	18 (40)	2 (22)	0.46
Rash requiring more than topical therapy (%)	5 (9)	5 (11)	0 (0)	0.58
Rejection[¥] (%)	1 (2)	0 (0)	1 (11)	0.17
Hospitalization (%)	18 (33)	14 (31)	4 (44)	0.46
Due to infection	8 (15)	7 (16)	1 (11)	1.00
Hepatic decompensation on treatment[€] (%)	13 (24)	10 (22)	3 (33)	0.67
Death (%)	6 (11)	5 (11)	1 (11)	1.00
Liver-related	6 (11)	5 (11)	1 (11)	1.00

[^] Reasons for treatment discontinuation not mutually exclusive.

[#] Hemoglobin < 8 in the first 16 weeks of the PI available in 53 patients.

[¥] Rejection on treatment or within one month of treatment discontinuation.

[€] Decompensating events included the development of ascites, encephalopathy or portal hypertensive bleeding.