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Journal

Journal of Hepatology, 61(3)

ISSN

0168-8278

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Publication Date

2014-09-01

DOI

10.1016/j.jhep.2014.04.037

Peer reviewed

HHS Public Access

Author manuscript

J Hepatol. Author manuscript; available in PMC 2015 September 01.

Published in final edited form as:

J Hepatol. 2014 September ; 61(3): 508–514. doi:10.1016/j.jhep.2014.04.037.

A US multicenter study of hepatitis C treatment of liver transplant recipients with protease-inhibitor triple therapy

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Abstract

Background & Aims—NS3/4A protease inhibitors, boceprevir or telaprevir, combined with peginterferon and ribavirin was the standard treatment for HCV genotype 1 and remains the only available direct antiviral drug based therapy in some countries. Efficacy and safety data in liver transplant recipients are limited.

Methods—This was a retrospective cohort study of 81 patients with genotype 1 HCV treated with boceprevir (10%) or telaprevir (90%) plus peginterferon and ribavirin at 6 US transplant centers (53% stage 3–4/4 fibrosis, 57% treatment experienced). The primary end point was undetectable HCV RNA 12 weeks after treatment completion (SVR12).

Results—The intent-to-treat SVR12 rate was 63% (51/81). Patients with an extended rapid virologic response, (undetectable HCV RNA at 4 and 12 weeks after starting boceprevir or telaprevir), had a higher rate of SVR12 than all other patients (85% vs. 15%, p <0.001). Adverse effects were common; 21% of patients experienced hemoglobin <8 g/dl and 57% required blood transfusions during the first 16 weeks. Twenty seven percent were hospitalized and 9% died; all were liver-related.

Conclusions—The addition of boceprevir or telaprevir to peginterferon and ribavirin yields SVR12 of 63% in liver transplant recipients with genotype 1 recurrent HCV, despite a high prevalence of advanced fibrosis and prior non-response to peginterferon and ribavirin. Rapid virologic response predicted a high likelihood of SVR. Despite a doubling of SVR rates, poor

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tolerability and high rates of adverse events were frequent and pose barriers to its widespread application.

Keywords

Telaprevir; Boceprevir; Antiviral therapy; Interferon; Ribavirin

Introduction

Recurrent hepatitis C virus (HCV) infection following transplantation results in 20–40% of patients having cirrhosis within 5-years, leading to graft loss and patient death [1–4]. The combination of peginterferon and ribavirin was the mainstay of treating recurrent HCV for nearly two decades but achieved sustained virological responses (SVR) of only ~30% (range 13–45%) of patients with HCV genotype 1 infection [5–7]. Triple therapy, using a NS3/4A protease inhibitor (PI), boceprevir or telaprevir, combined with peginterferon and ribavirin, increased the absolute rates of SVR by 30% in non-transplant patients [8–11] and these encouraging results suggested triple therapy might offer higher SVR rates for liver recipients.

Although, triple therapy with protease inhibitors was appropriately heralded as a breakthrough for improving virologic response, several concerns remained about use in transplant recipients. One of the major concerns was the potential for serious, even life-threatening, drug-drug interactions. Both boceprevir and telaprevir are strong inhibitors of cytochrome P450 3A4, the major route of metabolism of immunosuppressive medications [12,13], which could lead to excessive drug levels, excessive immunosuppression, and serious toxicity. Evaluation of HCV drugs that affect the metabolism of immunosuppressive agents is relevant for future drug combinations that may include CYP-3A4 inhibitors or inducers that may be used in transplant recipients.

The Consortium to Study Health Outcomes in HCV Liver Recipients (CRUSH-C) is a group of US academically based liver transplant centers focused on improving the outcomes of liver transplant recipients with recurrent HCV. In this report, CRUSH-C reports the efficacy and safety of PI-based triple therapy for HCV genotype 1 infected liver transplant recipients. This experience serves as the metric assessment by which future HCV therapies may be compared.

Patients and methods

Study design and patients

This is a retrospective cohort study of consecutive liver transplant recipients with recurrent genotype 1 HCV infection treated with either boceprevir- or telaprevir-based triple therapy at 6 large US liver transplant centers. Recurrent HCV was documented by the presence of HCV RNA and evidence of chronic hepatitis on liver biopsy. Patients with recent biopsy proven acute cellular rejection or medical contraindications to use of either interferon or ribavirin were not considered for treatment. The study conform to the ethical guidelines of

the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee to collect retrospective data.

A lead-in period of interferon and ribavirin was used in the majority of patients to determine the maximal tolerated doses of dual therapy before initiation of either boceprevir or telaprevir. Targets for this dose escalation were 180 μg weekly for peginterferon alfa-2a, 1.5 μg/kg weekly for peginterferon alfa-2b, or 12 μg daily for consensus interferon, and weight-based ribavirin adjusted for renal function and baseline hemoglobin. Patients with lead-in >90 days were excluded from this study to make the study population more comparable to approved treatment regimens. Generally, these excluded cases with long lead-in were virologic non-responders maintained on antiviral therapy while awaiting US Food and Drug Administration approval of boceprevir and telaprevir in May 2011. The choice of PI was at the investigator's discretion. Boceprevir (800 mg three times daily) was administered for 44 weeks in combination with peginterferon and ribavirin. Telaprevir (750 mg three times daily or 1125 mg twice daily) was used for 12 weeks followed by at least 32 weeks of interferon and ribavirin. Growth factor use was at the discretion of the investigator. Management of anemia was not standardized across centers, but the general approach at all centers was to use dose reduction as the first step in management, with introduction of erythropoietin (40,000 units weekly) when hemoglobin levels dropped <10 g/dl and blood transfusions for severe (hemoglobin <8 g/dl) and or symptomatic anemia. Immunosuppression and decision to transition patients from tacrolimus to cyclosporine prior to therapy was left to the investigators at each site. All patients had achieved a steady state of immunosuppression before antiviral therapy was started and dosing of the calcineurin inhibitor or mammalian target of rapamycin inhibitor during PI therapy aimed at maintaining steady state levels. Details of managing cyclosporine and tacrolimus [14] and rapamycin [15] drug-drug interactions have been previously described.

Study definitions

Plasma HCV RNA levels were quantified by COBAS TaqMan HCV RNA assay, version 2.0 (Roche) at all centers with minimum lower limit of quantification and detection of 43 IU/ml at 5 centers and 18 IU/ml at one center (27% of total patients). One site used a semi-automated real time polymerase chain reaction assay (Abbott) with lower limit of detection down to 12 IU/ml in a subset of their patients (17% of total patients). HCV RNA levels were measured prior to the initiation of interferon and ribavirin lead-in, prior to initiation of the PI and at weeks 4, 12, and 24 weeks after starting PI, at the end of treatment and 4 and 12 weeks after the end of treatment.

Extended rapid virologic response (eRVR) was defined as HCV RNA undetectable at 4 and 12 weeks (± 2 weeks) after initiation of PI. End of treatment response (EOTR) was defined as undetectable HCV RNA at end of therapy (± 4 weeks). Relapse was defined as post-treatment recurrence of detectable HCV RNA during the 12 weeks after completing therapy. Breakthrough was defined as emergence of detectable HCV RNA after being undetectable or >1 log increase in HCV RNA above nadir HCV RNA during treatment. Virologic failure for those receiving boceprevir was defined as HCV RNA >100 IU/ml after week 4 of receiving boceprevir or detectable HCV RNA at week 28, and for telaprevir was defined as

>1000 IU/ml at any time between weeks 4 through 12 after starting telaprevir or detectable HCV RNA at 24 weeks. It was left to the discretion of the investigator to continue interferon and ribavirin for those with virologic failure or breakthrough, however the PI was discontinued.

Efficacy assessments

The primary endpoint was the proportion of patients who achieved undetectable HCV RNA 12 weeks after completing antiviral therapy (SVR12, sustained virologic response at 12 weeks). All patients who received at least one dose of PI therapy were included. Data were complete for the primary endpoint. Secondary endpoints included rates of eRVR and EOTR. There were infrequent missing data for secondary endpoints (2 missing week 4 and week 12 after starting PI). In such cases missing viral loads were considered as positive.

Safety assessments

Chemical (e.g., serum creatinine) and hematologic (e.g., hemoglobin) assessments were recorded at baseline, PI initiation, weeks 2–4, week 8, 12, 16, end of therapy and 12 weeks after cessation of therapy. All hospitalizations including etiology, infectious complications, liver decompensation, blood transfusions, rejection episodes and deaths were recorded. Also collected was use of growth factors (erythropoietin, granulocyte colony-stimulating factor and eltrombopag), and dose reductions and discontinuations of interferon and ribavirin.

Statistical analysis

Baseline characteristics, virologic endpoints, immunosuppression management and safety components were described with frequencies (percent) or medians (range or interquartile range). Baseline characteristics were compared by leadin groups (≤30 days *vs*. >30 days of lead-in). Additional subgroup differences in virologic response, breakthrough and safety were also assessed. We evaluated the statistical significance of comparisons using the Fisher's exact or Wilcoxon rank sum tests, as appropriate. All analyses were completed using SAS version 9.3 (Cary, NC).

Results

Patients

From June 2011 through September 2013, a total of 125 patients received at least one dose of PI as part of triple therapy. Eighty-one patients had a lead-in ≤90 days, the potential for at least 44 weeks of triple therapy from start of PI, and at least 12 weeks of follow-up after treatment end and are the focus of this study. The baseline characteristics of the 81 patients are shown in Table 1. The median duration of treatment was 43 weeks (IQR 35–45). Nearly half (53%) had advanced fibrosis (F3–4) and 7% had severe cholestatic hepatitis. The majority of patients (57%) had failed prior antiviral therapy with peginterferon and ribavirin after liver transplantation.

Boceprevir was used in 8 (10%) and telaprevir in 73 (90%) patients. Peginterferon alpha-2a was used predominantly (96%) with peginterferon alpha-2b used in 4%. An interferon and ribavirin lead-in was utilized in 95% (77/81) of patients with 37% (30/81) of patients having

a standard 4 week lead-in (± 2 days) and 43% (35 of 81) with a lead-in >30 days. Median days of lead-in in this group was 42 days (IQR 35–65 days) compared to 28 days (IQR 22–28) in the group with ≤30 days of lead-in. No statistical differences in baseline characteristics were evident between those with ≤30 *vs*. >30 days of lead-in.

Efficacy

The overall rate of SVR12 was 63% (51/81). Early virologic responses are summarized in Fig. 1. SVR12 was similar between lead-in ≤30 day and lead-in >30 days (65% [30/46] *vs*. 60% [21/35]; $p = 0.65$). Patient characteristics associated with SVR12 are summarized in Table 2. The rate of relapse was 9% (5/56). Most relapses (80%) occurred by 4 weeks post-treatment. All 29 patients that achieved SVR12 and by 24 weeks of follow-up remained HCV RNA negative. SVR12 was achieved in 3 of 6 (50%) patients with severe cholestatic hepatitis.

The effect of early virologic response on SVR12 is summarized in Fig. 2. There was no difference in early virologic response (>1 log drop in HCV RNA) between those with lead-in ≤30 days *vs*. lead-in of 31–90 days (63% (27/43) vs. 58% (18/31); $p = 0.81$). Patients with detectable HCV RNA at week 4, but undetectable at week 12 were more likely to experience virologic break-through when the PI was discontinued (44% [4/9]) compared to patients with undetectable HCV RNA at weeks 4 and 12 (9% [5/55]); $p = 0.02$. No patient with detectable HCV RNA at week 12 of PI therapy achieved SVR12.

Management of Immunosuppression and rejection

In boceprevir treated patients, median cyclosporine doses were 225 mg per day at baseline and were reduced to median 75 mg per day by week 4 of boceprevir therapy (66% reduction; N = 2). Median tacrolimus doses in those on boceprevir were 1.5 mg per day at baseline and were reduced to a median of 0.25 mg per day (dosed every 1–2 weeks) by week 4 of boceprevir therapy (88% reduction; N = 5). In telaprevir treated patients, median cyclosporine doses were 200 mg per day at baseline and were reduced to a median of 50 mg per day by week 4 of telaprevir therapy (68% reduction; N = 52). Median tacrolimus doses were 1 mg per day at baseline and were reduced to a median of 0.5 mg per day (dosed every 1–2 weeks) by week 4 of telaprevir therapy (75% reduction; N = 11).

Two patients experienced biopsy proven acute cellular rejection of the liver during treatment at 25.4 and 22.6 weeks after starting telaprevir. Antiviral therapy was discontinued in both. One of 3 simultaneous liver-kidney transplant recipients experienced renal allograft rejection 20.6 weeks after starting telaprevir and antiviral therapy was discontinued. All three were on tacrolimus and responded to corticosteroid pulses and adjustment in maintenance immunosuppression; there was no steroid resistant rejection or any immunologic graft losses.

Safety

Table 3 summarizes adverse events in this study. Renal dysfunction, defined as an increase in serum creatinine of P0.5 mg/dl from baseline during the first 16 weeks of PI-triple therapy occurred in 38% of patients. The median increase in serum creatinine from baseline

during treatment was 0.4 mg/dl (IQR 0.3–0.6). No patients receiving rapamycin (0 of 6) had a >0.5 mg/dl increase in serum creatinine during the first 16 weeks (p = 0.08). There were no consistent correlations between renal function (serum creatinine and estimated glomerular filtration rate) and calcineurin inhibitor doses and trough levels. Anemia was a frequent and significant side effect. During the first 16 weeks after starting the PI, 21% (17/81) experienced a decline in hemoglobin to <8 g/dl and erythropoietin was used in 81% of patients. Transfusions of packed red blood cells was required in 57% (46/81) with a median of 4 units (IQR 2–8) per patient transfused. There were no statistical differences in renal or anemia side effects between those with ≤30 days and >30 days of lead-in but interferon dose interruptions were more frequent in those with >30 days of lead-in (22.9% vs. 6.5% in those with lead-in ≤30 days; $p = 0.049$).

The overall rate of hospitalization was 27% (22/81) with hospitalization for infectious complications occurring in 50% (11/22). Adverse events leading to early discontinuation of therapy occurred in 15% (12/81) with the most common reasons (>1 reason possible per patient) being anemia in 2, decompensated cirrhosis in 2, allograft rejection in 3 (2 liver, 1 kidney), bacteremia in 2 and thrombocytopenia in 1. Rash requiring more than topical therapy was uncommon occurring in only 11% (9/81) of patients.

There were 7 deaths during the study; all were liver-related. Four patients had advanced fibrosis (stage 3–4) pretreatment and 1 had severe cholestatic hepatitis. All 7 patients had detectable viral load at time of death (4 virologic breakthroughs, 1 virologic relapse after completing therapy and 2 without ever achieving undetectable HCV RNA). In addition, 5 out of 7 had adverse events leading to early discontinuation, including 2 patients who experienced liver allograft rejection during treatment and 3 patients who developed hepatic decompensation with ascites and acute renal failure while receiving PI.

Discussion

This large multicenter experience of PI-based triple therapy for recurrent HCV genotype 1 in liver transplant recipients found an SVR12 rate of 63%, representing an approximately 2-fold higher rate of viral eradication than has historically been achieved with peginterferon and ribavirin alone [7,8,16]. These results are even more impressive given the ‘‘difficult to cure’’ characteristics of this patient population. Treatment was undertaken in patients with the greatest need for viral clearance, as reflected by the high proportion of patients with advanced liver disease, many of who were felt to have poor short-term prognosis without therapy. However, we also have demonstrated that this improvement in SVR comes with significant challenges in management including navigation of drug-drug interactions and associated hematologic and renal toxicities.

Early virologic response was highly predictive of SVR. Those experiencing eRVR had a higher rate of SVR12 (85% with eRVR vs. 15% with no eRVR; $p < 0.001$). Patients with detectable HCV RNA at week 4, but negative at week 12 were more likely to experience virologic breakthrough compared to those negative at both weeks 4 and 12 (44% vs. 9%, $p = 0.02$). No patient achieved SVR who had detectable HCV RNA at 12 weeks. Based upon our results, we propose that detectable HCV RNA at PI treatment week 12 serves as a

futility rule for transplant recipients receiving treatment with boceprevir- or telaprevir-based triple therapy. A majority (53%) of patients in this study utilized an HCV RNA assay with a lower limit of detection down to 43 IU/ml. With use of a more sensitive assay, rates of eRVR and its predictive value on virological breakthrough and SVR12 could be impacted. However, differences in HCV RNA assays do not affect the accuracy of the primary endpoint of SVR12.

The multiple drug-drug interactions of boceprevir and telaprevir have been well described [17]. Prior to initiation of this study, the interaction between HCV PIs and calcineurin inhibitors was only studied in healthy volunteers [12,13]. When treating recurrent HCV with boceprevir and telaprevir close monitoring of immunosuppressive drug levels is required throughout the period of PI treatment; however, there are two critical time periods requiring hypervigilance: (1) At PI initiation and (2) At PI discontinuation. Many investigators in this study switched to cyclosporine to decrease the magnitude of drug-drug interactions and because prior studies with peginterferon and ribavirin therapy suggested higher rates of SVR in patients on maintenance immunosuppression with cyclosporine vs. tacrolimus [18,19]. Our study did find a statistically higher SVR in patients receiving cyclosporine vs. tacrolimus (38/55 [69%] vs. 7/17 [41%]; $p = 0.048$). Thus, the decision on choice of PI and calcineurin inhibitor should consider this finding taking into consideration the physician's experience with the specific drugs in the transplant setting.

As in other reports on the safety of PI-triple therapy [20,21], we found that anemia was common in liver recipients and required near uniform ribavirin dose reduction, frequent need for erythropoietin, and despite these appropriate interventions, blood transfusions were frequently required. As we only assessed anemia during the first 16 weeks of therapy, the impact of anemia with PI-based triple therapy is likely even greater than we report. In addition to the known effects of peginterferon, ribavirin, and telaprevir/boceprevir, contributing factors to anemia in liver transplant recipients include baseline renal insufficiency, cyclosporine based-immunosuppression, low baseline hemoglobin values and mycophenolate mofetil use [22,23]. Given the high prevalence of anemia, lower starting doses of ribavirin should be considered and earlier and/or lower thresholds for ribavirin dose reduction and initiation of erythropoietin should be considered in patients receiving PI-based antiviral therapy. Future therapies with next generation PIs are expected to reduce the frequency and severity of anemia, as will treatment combinations that are interferon-free and/or ribavirin-free.

Another frequent side effect seen in liver transplant patients on triple therapy was renal dysfunction. Renal dysfunction has been recently reported in both boceprevir and telaprevir treated patients in the pre-transplant setting [24]. A similar effect was seen in our study, with the association likely exaggerated due to concurrent calcineurin inhibitor administration. Interestingly, we observed no significant change (>0.5 mg/dl from baseline) in serum creatinine in the 6 patients receiving rapamycin, further implicating the calcineurin inhibitor. The renal effect may or may not be due to altered calcineurin inhibitor metabolism via inhibition of cytochrome P450 3A4 by the PI. An alternative explanation could be PI inhibition of P-glycoprotein. Calcineurin inhibitors and other drugs are extruded from renal tubular cells by the efflux pump, P-glycoprotein. Inhibition of P-glycoprotein by PI could

increase intracellular concentrations of calcineurin inhibitors within renal tubular cells increasing risk for nephrotoxicity. Our findings highlight the need for more pharmacokinetic studies of the current and future direct acting antiviral (DAA) agents in the transplant population.

Death was not a rare event in this study, occurring in 7 (9%) patients, with all death related to liver failure. Of the 7 liver related deaths, liver allograft rejection occurred in 2 patients. Given the detrimental effects of treating acute cellular rejection with corticosteroids [25,26], the treatment of rejection may have contributed to these deaths. Another 2 deaths occurred in patients with decompensated cirrhosis with ascites at baseline who developed acute renal failure while receiving PI. Given the previously mentioned association of the PI with renal dysfunction, it is possible that the PI contributed to the development of renal failure and their subsequent deaths.

Two new DAAs, sofosbuvir and simeprevir, have recently been approved by the FDA for treatment of chronic HCV in combination with pegylated interferon and ribavirin. Both offer advantages over boceprevir- and telaprevir-based therapy in that there are limited drug interactions and fewer side effects. Additionally, encouraging preliminary data on interferon-free multi-DAA combinations are emerging and promise to enhance rates of SVR, reduce toxicity, improve tolerability and compliance, and limit drug-drug interactions (Charleton MR, *et al*. presented at 64th Annual Meeting of American Association for Study of Liver Disease). However, in many countries in the world performing transplantation, these new drug therapies will not be available for some time and telaprevir or boceprevir in combination with peginterferon and ribavirin may be the best treatments available. For those transplant physicians, the results from our study will aid in decision-making and help with patient management.

In summary, we have shown that PI-based triple therapy achieves cure in 63% of liver transplant recipients. However, these cure rates come with a high “cost” in terms of adverse events including anemia, renal dysfunction and death. Future therapies using interferon-free multi-DAA regimens may improve rates of SVR, lower toxicity, and offer fewer drug-drug interactions. Current treatment and the promise of improved future therapies offer hope for the liver transplant recipient burdened by recurrent HCV infection.

Acknowledgement

The study was supported by the UCSF Liver Center Biostatistics Core (P30 DK026743).

Conflict of interest

James R. Burton, Jr.: Vertex: Research grant support.

Jacqueline G. O’Leary: Vertex: Speakers bureau, consulting.

Gregory T. Everson: Vertex: Research grant support, advisory boards, Merck: Research grant support, advisory boards, Roche/: Research grant support, advisory boards.

Robert S. Brown Jr: Vertex: Research grant support, consulting, Merck: Research grant support, consulting, Roche/Genentech: Consulting.

Norah A. Terrault: Vertex: Research grant support, advisory board, Merck: Advisory board, Roche/Genentech: Consulting.

Abbreviations

HCV	hepatitis C virus
SVR	sustained virological response
PI	protease inhibitor
CRUSH-C	The Consortium to Study Health Outcomes in HCV Liver Recipients
HCV RNA	hepatitis C virus ribonucleic acid
eRVR	extended rapid virological response
EOTR	end of treatment response
SVR12	undetectable HCV RNA 12 weeks after treatment completion
DAA	direct activing antiviral

References

1. 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]
2. Yilmaz N, Shiffman ML, Stravitz RK, Sterling RK, Luketic VA, Sanyal AJ, et al. A prospective evaluation of fibrosis progression in patients with recurrent hepatitis C virus following liver transplantation. Liver Transpl. 2007; 13:975–983. [PubMed: 17600360]
3. Carrion JA, Torres F, Crespo G, Miquel R, Garcia-Valdecasas JC, Navasa M, et al. Liver stiffness identified two different patterns of fibrosis progression in patients with hepatitis C virus recurrence after liver transplantation. Hepatology. 2010; 51:23–34. [PubMed: 19839063]
4. 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]
5. Wang CS, Ko HH, Yoshida EM, Marra CA, Ricardson K. Interferon-baed combination antiviral therapy for hepatitis C virus after liver transplantation: a review an quantitative analysis. Am J Transpl. 2006; 6:1586–1599.
6. 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]
7. 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]
8. 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; 364:1207–1217. [PubMed: 21449784]
9. 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]
10. Zeuzem S, Andrenone P, Pol S, Laawitz E, Diego M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011; 364:2417–2428. [PubMed: 21696308]
11. 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]

12. 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]
13. Hulskotte E, Gupta S, Xuan F, van Zutven M, O'mara E, Fent HP, et al. Pharmacokinetic interaction between hepatitis C virus protease inhibitor boceprevir and cyclosporine and tacrolimus in healthy volunteers. Hepatology. 2012; 56:1622–1630. [PubMed: 22576324]
14. Coilly A, Roche B, Duclos-Vallee JC, Samuel D. Management of HCV transplant patients with triple therapy. Liver Int. 2014; 34:46–52. [PubMed: 24373078]
15. 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]
16. Berenguer M, Palau A, Fernandez A, Benlloch S, Aguilera V, Prieto M, et al. Efficacy, predictors or response, and potential risks associated with antiviral therapy in liver transplant recipients with recurrent hepatitis C. Liver Transpl. 2006; 12:1067–1076. [PubMed: 16622844]
17. Kiser JJ, Burton JR, Anderson PL, Everson GT. Review and management of drug interactions with boceprevir and telaprevir. Hepatology. 2012; 55:1620–1628. [PubMed: 22331658]
18. Firpi RJ, Soldevila-Pico C, Morelli GG, Cabrera R, Levy C, Clark VC, et al. The use of cyclosporine for recurrent hepatitis C after liver transplant: a randomized pilot study. Dig Dis Sci. 2010; 55:196–203. [PubMed: 19798576]
19. Rabie R, Mumtaz K, Renner EL. Efficacy of antiviral therapy for hepatitis c after liver transplantation with cyclosporine and tacrolimus: a systematic review and meta-analysis. Liver Transpl. 2013; 19:46–48.
20. Coilly A, Roche B, Dumortier J, Leroy V, Botta-Fridlund D, Radenne S, et al. Safety and efficacy of protease inhibitors to treat hepatitis C after liver transplantation, a multicenter experience. J Hepatol. 2014; 60:78–86. [PubMed: 23994384]
21. Pungpapong S, Aqel BA, Koning L, Murphy JL, Henry TM, Rylan KL, et al. Multicenter experience using telaprevir or boceprevir with peginterferon and ribavirin to treat hepatitis C genotype 1 after liver transplantation. Liver Transpl. 2013; 19:690–700. [PubMed: 23696372]
22. Giusto M, Rodriguez M, Navarro L, Rubin A, Aguilera V, San-Juan F, 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; 17:1318–1327. [PubMed: 21761553]
23. Hodo Y, Tsuji K, Mizukoshi E, Yamashita T, Sakai A, Nakamoto Y, et al. Pure red cell aplasia associated with concomitant use of mycophenolate mofetil and ribavirin in post-transplant recurrent hepatitis C. Transpl Int. 2006; 19:170–171. [PubMed: 16441367]
24. Mauss S, Hueppe D, Alshuth U. Renal impairment is frequent in chronic hepatitis C patients under triple therapy with telaprevir or boceprevir. Hepatology. 2014; 59:46–48. [PubMed: 23813604]
25. Charlton M, Seaberg E, Wiesner R, Everhart J, Zetterman R, Lake J, et al. Predictors of patient and graft survival following liver transplantation for hepatitis C. Hepatology. 1998; 28:823–830. [PubMed: 9731579]
26. Prieto M, Berenguer M, Rayon JM, Cordoba J, Arguello L, Carrasco D, et al. High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: relationship with rejection episodes. Hepatology. 1999; 29:250–256. [PubMed: 9862874]

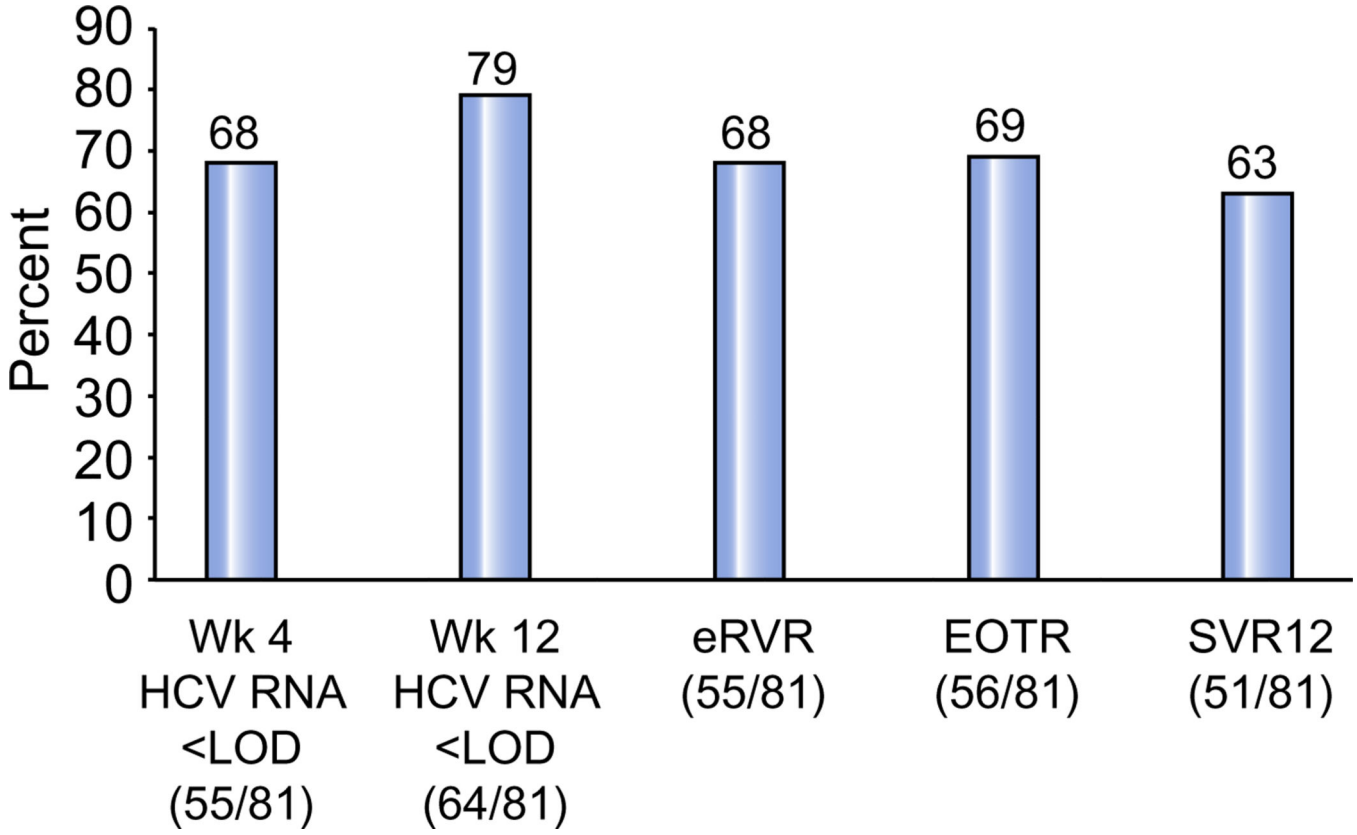

Fig. 1. Early (week 4 and 12), end of treatment and 12 week sustained virologic response with protease inhibitor-based triple therapy are depicted

<LOD, below level of detection; eRVR, extended rapid virologic response HCV RNA below level of detection at 4 and 12 weeks after starting protease inhibitor; EOTR, end of treatment response, HCV RNA below level of detection at end of therapy; SVR12, sustained virologic response at 12 weeks after stopping therapy.

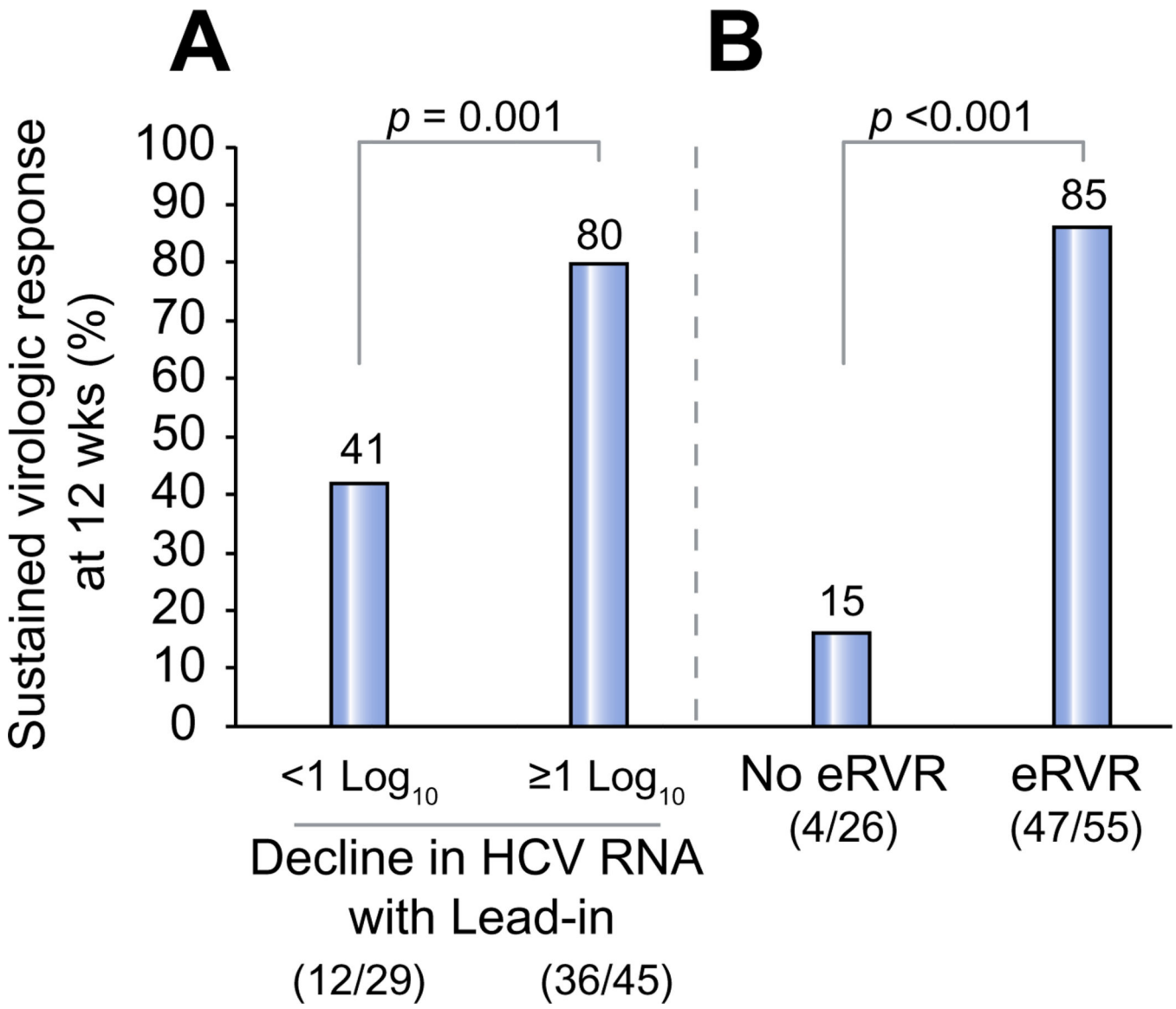

Fig. 2. Early virologic response predictors of 12 week sustained virologic response (SVR12)

(A) Virologic response with interferon and ribavirin lead-in prior to starting protease inhibitor and (B) extended rapid virological response (eRVR; HCV RNA negative at week 4 and 12 after starting protease inhibitor).

Table 1

Baseline characteristics.

Recipient characteristic	**n = 81**
Years of age at baseline, median (range)	58 (35–73)
Male sex, no. (%)	62 (76)
Years from transplant to start of PI, median (range)	4.3 (0.5–17.9)
Race or ethnic group, no. (%)	
White	51 (63)
Black	7 (9)
Asian or other	3 (4)
Hispanic	20 (25)
HCV genotype, no. (%)	
1a	45 (56)
1b	33 (41)
1 (subtype unknown)	3 (4)
HCV RNA (log_{10}) prior to P/R*, median (IQR)	6.6 (5.8–6.9)
HCV RNA >800,000 IU/ml*, no. (%)	56 (71)
Interleukin-28B genotype#	
CC, no. (%)	14 (30)
Non-CC, no. (%)	33 (70)
Fibrosis stage%	
F0–2, no. (%)	38 (47)
F3–4, no. (%)	43 (53)
Cholestatic hepatitis, no. (%)	6 (7)
Prior antiviral therapy post-transplant	
Null, no. (%)	23 (28)
Partial, no. (%)	11 (14)
Relapse, no. (%)	12 (15)
None, no. (%)	35 (43)
Immunosuppression at time of P/R lead-in	
Cyclosporine, no. (%)	55 (68)
Tacrolimus, no. (%)	17 (21)
Mycophenolate mofetil or mycophenolic acid, no. (%)	62 (76)
Rapamune, no. (%)	6 (7)
Steroids, no. (%)	23 (28)
Labs$, median (IQR)	
Total bilirubin, mg/dl	1.5 (0.8–2.0)
Creatinine, mg/dl	1.2 (1.0–1.4)
Serum albumin, mg/dl	3.6 (3.3–4.0)

Recipient characteristic	n = 81
Hemoglobin, g/dl	11.8 (10.3–12.9)
Platelets, per mm^3	121 (92–164)
International normalization ratio	1.0 (1.0–1.1)

PI, protease inhibitor; P, (peg)interferon; R, ribavirin.

*Baseline HCV RNA prior to start of interferon and ribavirin available in 79/81.

#Interleukin-28B 12979860 polymorphism information available in 47/81.

%Batts-Ludwig scoring system.

$All laboratory results at start of protease inhibitor, except platelets which is at start of interferon and ribavirin. Hemoglobin values available in 80/81 and international normalization ratio available in 49/81.

Table 2

Sustained virologic response by patient characteristics.

Subgroup and end-points	Number/total number (%)
All patients	51/81 (63)
>1 $\log_{10}$ drop in HCV RNA with lead-in	36/45 (80)*
Patients with undetectable viral load#	
At 4 wks	47/55 (85)**
At 12 wks	51/64 (80)**
At both wks 4 and 12	47/55 (85)**
Fibrosis	
F0–2	29/38 (76)
F3–4	22/43 (51)*
Genotype	
1a	24/45 (53)
1b	25/33 (76)
HCV RNA levels at baseline	
≤800,000 IU/ml	16/23 (70)
>800,000 IU/ml	35/56 (62)
Interleukin-28B phenotype	
CC	9/14 (64)
Non-CC	19/33 (58)
Race	
White	33/51 (65)
Black	4/7 (57)
Calcineurin-inhibitor	
Cyclosporine	38/55 (69)
Tacrolimus	7/17 (41)*

* p <0.05 and

** p <0.001.

Minimum lower limit of quantification and detection of 43 IU/ml in 56%, 18 IU/ml in 27% and 12 IU/ml in 17% of total patients.

Table 3

Adverse events.

Adverse event	n = 81
Anemia	
Starting dose ribavirin (mg), median (IQR)	600 (400–800)
Minimum dose ribavirin (mg), median (IQR)	400 (200–400)
Maximum dose ribavirin (mg), median (IQR)	800 (600–1000)
Lowest hemoglobin during first 16 weeks after starting PI	
<8 mg/dl, no. (%)	17 (21)
8–10 mg/dl, no. (%)	46 (57)
>10 mg/dl, no. (%)	18 (22)
Received red blood cell transfusion*, no. (%)	46 (57)
Units transfused per patient, median (IQR)	4 (2–8)
Dose reduction of ribavirin, no. (%)	70 (86)
Ribavirin dose interruption, no. (%)	56 (69)
Use of erythropoietin, no. (%)	66 (81)
Initiation time in days#, median (IQR)	39 (26–70)
Leukopenia	
Dose reduction of interferon, no. (%)	31 (38)
Interferon dose interruption, no. (%)	11 (14)
Use of granulocyte-colony stimulating factor, no (%)	38 (47)
Initiation time in days#, median (IQR)	34 (20–87)
Thrombocytopenia	
Use of eltrombopag, no. (%)	3 (4)
Initiation time in days#, median (IQR)	50 (34–116)
Renal insufficiency	
Serum creatinine >0.5 mg/dl increase from baseline*	31 (38)
Increase in creatinine (mg/dl), median (IQR)*	0.4 (0.3–0.6)
Rash requiring more than topical therapy, no. (%)	9 (11)
Hospitalizations	22 (27)
Hospitalizations for infection%	11 (14)
Adverse event leading to early discontinuation of treatment	12 (15)
Acute cellular rejection requiring corticosteroids	
Liver, no. (%)	2 (2)
Kidney$, no. (%)	1 (33)
Death, no. (%)	7 (9)
Liver-related, no. (%)	7 (9)
Non-liver related, no. (%)	0 (0)

[*] During first 16 weeks after start of protease inhibitor.

[#] From start of interferon and ribavirin lead-in.

[%] Data only available for 79 patients.

[$] Percentage based on 3 simultaneous liver-kidney transplant patients were treated with triple therapy.