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Sofosbuvir and Simeprevir for Treatment of Hepatitis C Virus Infection in Liver Transplant Recipients

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Abstract

Recurrent hepatitis C virus (HCV) infection occurs universally in the allograft in the absence of effective antiviral therapy before liver transplantation (LT). Antiviral therapy with sofosbuvir and simeprevir has proven to be highly effective and well tolerated in the nontransplant setting for treatment of HCV genotype 1 infection; therefore, we sought to evaluate the efficacy and safety of this regimen in LT recipients with recurrent HCV infection. This was a retrospective analysis of a single-center treatment protocol of patients with HCV genotype 1 infection who received a 12-week combination regimen of sofosbuvir and simeprevir. Sixty-one patients (35 with genotype 1a and 26 with genotype 1b) completed treatment with simeprevir and sofosbuvir. Three patients received additional ribavirin. Laboratory data and clinical assessments performed at the baseline, on treatment, at the end of treatment, and 12 weeks after the completion of antiviral therapy [sustained virological response at 12 weeks (SVR12)] were analyzed. The median time after LT was 5.4 years [interquartile range (IQR), 1.9-8.4 years], and tacrolimus was the most commonly used immunosuppressive agent (80.3%). Overall, SVR12 was achieved in 93.4% [95% confidence interval (CI), 84%-97%] of LT recipients treated with 12 weeks of sofosbuvir and simeprevir. When they were analyzed according to the HCV subtype, LT recipients with genotype 1b had a 100% SVR12 rate (95% CI, 87%-100%), whereas SVR12 was 89% (95% CI, 74%-95%) for those with genotype 1a. Advanced fibrosis (METAVIR F3-F4) was associated with diminished antiviral efficacy in LT recipients with genotype 1a [SVR12, 67% (95% CI, 39%-86%); P 5 0.01]. Overall, the incidence of adverse events (AEs) was low, and no severe AEs occurred during treatment. In conclusion, treatment with a 12-week regimen of sofosbuvir and simeprevir was well tolerated and resulted in a high SVR12 rate for LT recipients with recurrent HCV genotype 1 infection. Genotype 1a patients with advanced fibrosis of the allograft were more likely to relapse.

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Hepatitis C virus (HCV) infection remains the most common etiology for end-stage liver disease and is the leading indication for liver transplantation (LT) in the United States.[1] In the absence of successful antiviral therapy and a sustained virological response (SVR) before LT, recurrent HCV infection occurs nearly universally in the allograft and is associated with rapid progression of fibrosis, which results in reduced patient and allograft survival.[2,3] Cirrhosis of the allograft due to recurrent HCV infection occurs in approximately 50% of LT recipients within 5 years, and overt hepatic decompensation occurs in 33% of LT recipients after 1 year of development of cirrhosis.[4] Furthermore, recurrent HCV infection in LT recipients is responsible for 25% to 30% of all hepatic allograft losses.[3,5]

SVR in LT recipients is associated with improved outcomes, including stabilization and regression of fibrosis.[6,7] However, antiviral therapy in this population was difficult up until recent times, particularly because of frequent adverse events (AEs) and significant drug-drug interactions, with overall poor efficacy of previous regimens containing interferon and ribavirin. Data from a systematic review showed a pooled SVR of 29% after treatment for 48 weeks with pegylated interferon and ribavirin for recurrent HCV genotype 1 infection in LT recipients. Furthermore, toxicity was common, and dose reductions and discontinuation of therapy were required in 73% and 28% of individuals, respectively.[8] The addition of boceprevir or telaprevir to interferon and ribavirin in this population resulted in SVR rates of up to 58% and 71%, respectively; however, increased toxicity occurred (most commonly cytopenias), and this resulted in ribavirin dose reductions in up to 93% of patients, the need for erythropoiesis-stimulating agents in up to 97% of patients, and red cell transfusions in up to 53% of patients.[9-11] Boceprevir and telaprevir are potent inhibitors of the cytochrome P450 isoenzymes cytochrome P450 3A4/5 and cytochrome P450 3A, respectively, and coadministration of tacrolimus, cyclosporine, and sirolimus results in increased plasma levels of these immunosuppressants.

New and emerging HCV treatment regimens employing all-oral combinations of direct-acting antiviral agents markedly improve tolerability and efficacy. Sofosbuvir is an oral nonstructural protein (NS) 5B nucleotide polymerase inhibitor, and it is highly effective for the treatment of HCV genotypes 1, 2, 3, 4, 5, and 6.[12-14] Simeprevir is an oral inhibitor of the NS 3/4A protease with well-documented efficacy against HCV genotype 1.[15-17] Sofosbuvir was studied in combination with ribavirin for the treatment of recurrent HCV infection in LT recipients. Overall, SVR was achieved in 67% of LT recipients with HCV genotype 1 infection (73% in subtype 1a and 54% in subtype 1b). Severe anemia (hemoglobin < 10 g/dL) occurred in one-third of individuals, and 20% required erythropoietin.[18] The combination of sofosbuvir and simeprevir allows an interferon/ribavirin-free, all-oral antiviral regimen that is highly effective and well tolerated in individuals with and without cirrhosis who have not undergone LT.[19] These encouraging results have led many LT centers, including ours, to use this antiviral regimen for the treatment of HCV infection in LT recipients; therefore, we sought to evaluate the efficacy and safety of sofosbuvir and simeprevir in LT recipients with recurrent HCV genotype 1 infection with different stages of fibrosis of the allograft.

PATIENTS AND METHODS

Study Design and Patients

This was a retrospective analysis of a single-center treatment protocol of LT recipients with recurrent HCV genotype 1 infections who received sofosbuvir and simeprevir (with or without additional ribavirin). Inclusion criteria included an age greater than 18 years, an estimated glomerular filtration rate with the Modification of Diet in Renal Disease equation greater than 30 mL/ minute, and a stable immunosuppressive regimen for 3 months before the initiation of antiviral therapy (unless the patient was suspected of having fibrosing cholestatic hepatitis). Patients were also required to have a liver biopsy for staging of the disease within 2 years unless a previous biopsy had shown METAVIR stage 3 or 4. Radiological evidence of cirrhosis was also satisfactory for staging. Individuals who met the inclusion criteria at the time of a posttransplant clinic visit at the Miami Transplant Institute were consecutively enrolled in our HCV treatment protocol for LT recipients. The treatment protocol was established after the US Food and Drug Administration (FDA) had licensed sofosbuvir and simeprevir individually for the treatment of HCV infection in nontransplant populations. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki with approval by the institutional review board at the University of Miami.

Antiviral Regimen

LT recipients with recurrent HCV genotype 1 infections were treated with 400 mg of sofosbuvir orally once daily and with 150 mg of simeprevir orally once daily with or without additional ribavirin (1000 mg orally daily in individuals with a body weight less than 75 kg or 1200 mg orally daily in those with a body weight of 75 kg or greater) for a total of 12 weeks. The addition of ribavirin, dose adjustments, or discontinuation of this agent was at the discretion of the treating hepatologist. Compliance with antiviral therapy was monitored through the 12 weeks of treatment by LT coordinators through routine telephone encounters, by pharmacists through reviews of the filling of monthly refills of medications, and with transplant hepatologists during scheduled clinic visits.

Follow-Up and Outcomes

Individuals were followed closely during treatment with scheduled clinic appointments with LT coordinators and transplant hepatologists. Additional follow-up for 12 weeks after the completion of antiviral treatment was performed to evaluate the sustained virological response at 12 weeks (SVR12). Protocol laboratory testing was obtained at 4-week intervals and included complete blood cell counts, serum electrolytes, a renal function panel, liver chemistries, and serum levels of immunosuppressive agents. In addition, plasma samples were tested for quantitative HCV RNA by the polymerase chain reaction technique with the COBAS TaqMan assay (version 2; Roche, Pleasanton, CA; lower limit of detection, 15 IU/mL) every 4 weeks during treatment, at the end of treatment (EOT), and 12 weeks after the completion of treatment (SVR12). The primary outcomes of this study were the proportion of LT recipients achieving SVR12 and the incidence of AEs associated with the antiviral agents. Secondary outcomes were changes in liver chemistries during and after the completion of antiviral therapy, changes in the dose of immunosuppressive agents, and changes in serum levels during and after the completion of antiviral therapy.

Safety Assessment

Blood work, including complete blood cell counts, electrolytes, renal function, and liver chemistries, was monitored during and after treatment at 4-week intervals as part of the treatment protocol. Individuals were also asked during each visit about potential AEs to antiviral therapy and had direct telephone access to post-LT coordinators to address concerns about AEs.

Statistical Analysis

An initial sample size calculation was not performed because this was a retrospective analysis of previously recorded data. All data were analyzed with SAS JMP (SAS, Cary, NJ). Fisher's exact test was used to analyze categorical variables; a P value < 0.05 was considered significant.

RESULTS

Sixty-one patients were included in the study; baseline demographic and clinical characteristics are shown in Table 1. All patients were at least 3 months after LT when started antiviral therapy, and 1 patient was treated 17 years after LT; the median time after LT was 5.4 years [interquartile range (IQR), 1.9-8.4 years]. Most patients were white and male, and the median age was 61 years (IQR, 58-65 years). Genotype 1a accounted for 57% of patients, and genotype 1b accounted for 43%. Two patients had fibrosing cholestatic hepatitis. No patients included in this analysis discontinued antiviral therapy early, and only 1 patient had an interruption of therapy for 1 week because of urosepsis (unrelated to hepatic decompensation or drug-related AEs). Three patients were started on ribavirin at the initiation of therapy but stopped it at week 4. In 1 case, ribavirin was stopped because of anemia, whereas in the other 2 patients, it was stopped because of poor tolerability at the discretion of the hepatologist. No data were collected on the Q80K polymorphism or the *IL28B* genotype.

Overall, 57 [93.4%; 95% confidence interval (CI), 83%-97%] of the treated patients achieved SVR12. No patient experienced a virological breakthrough on treatment; 4 patients relapsed after treatment. In separate assessments of patients by genotype 1 subtype, 26 patients (100%; 95% CI, 87%-100%) with genotype 1b achieved SVR, and they included 11 patients with advanced fibrosis (METAVIR F3-F4). In contrast, 89% (95% CI, 74%-95%) of patients with HCV genotype 1a achieved SVR. The SVR rate was 100% (95% CI, 85%-100%) for the 23 patients with genotype 1a and early fibrosis (METAVIR F1-F2); however, significantly lower SVR rates were seen for genotype 1a patients with advanced fibrosis versus early fibrosis (P 5 0.01). In total, 8 of 12 patients (67%; 95% CI, 39%-86%) with HCV genotype 1a and METAVIR F3-F4 attained SVR.

Forty-one patients (67.2%) had a rapid virological response (RVR), and 58 (95%) had undetectable HCV RNA by week 8 of treatment. There were no significant differences when we examined variations in viral kinetics at week 4 or 8 by HCV subtype. Overall, more patients with advanced fibrosis or cirrhosis had detectable HCV RNA at week 4 in comparison with patients with early fibrosis (P 5 0.02). However, when the analysis was

performed by both HCV subtype and stage of fibrosis, this association was significant only among patients with genotype 1a (see Table 2).

Because relapse was observed only in patients infected with genotype 1a with METAVIR F3-F4, we further examined this subset's baseline characteristics to identify variables associated with SVR versus relapse (see Table 3). Of the 4 patients who relapsed, 1 had been diagnosed with fibrosing cholestatic hepatitis. This patient temporarily interrupted treatment for 1 week because of urosepsis that required admission to the intensive care unit and ultimately experienced graft failure (from progressive liver disease); the patient died of multiorgan failure 4 months after the completion of antiviral therapy. The other patient with fibrosing cholestatic hepatitis in the study also had genotype 1a and advanced fibrosis but achieved SVR12. All 3 female patients with genotype 1a with METAVIR F3-F4 attained SVR12, and the 4 patients who relapsed were male (P 5 0.49). Two of 3 patients with decompensated liver disease, defined as the presence of ascites, gastroesophageal varices, or hepatic encephalopathy, relapsed. Four individuals had baseline total bilirubin levels > 1.5 mg/dL, and 3 of those relapsed (P 5 0.06). Eleven (91.7%) of the 12 patients with genotype 1a with METAVIR F3-F4 were treatment-experienced; the single treatment-naive patient did not attain SVR12. Three patients were previously treated with telaprevir, and 1 of those patients relapsed. None of the patients in this group received ribavirin during the 12 weeks of therapy. Three of the 4 patients who relapsed were treated with immunosuppressive regimens that did not contain tacrolimus (1 with cyclosporine and 2 with sirolimus). No data were available about the prevalence of the Q80K polymorphism in our studied population.

Treatment was generally well tolerated. AEs were recorded in 54% of the patients, with no significant differences between those with early and advanced fibrosis, as shown in Table 4. The most common AEs were fatigue (27.9%), headache (18%), and nausea (9.8%). Only 3.3% of the patients had a significant decrease in hemoglobin levels (<10 g/dL). Rash (of any type) and photosensitivity were reported in a minority of patients and did not lead to treatment interruption or discontinuation. Simeprevir is a known inhibitor of the hepatic organic anion-transporting polypeptide (OATP1B1) and multidrug resistance-associated protein (MRP2) (also called canalicular multispecific organic anion transporter 1), and thus hyperbilirubinemia may occur in patients receiving this agent; however, we found that only 3.3% of patients had an elevation of bilirubin > 1 mg/dL on therapy. Deterioration of renal function (defined by an increase in creatinine >0.5 mg/dL) occurred in 8.2% of patients. Grade 3 or 4 AEs tended to occur more commonly in patients with advanced fibrosis (5.3% versus 17.4%; P 5 0.18). No patients died during therapy, although 2 patients died shortly after SVR12 [one with sepsis and multiorgan failure and the other with recurrent hepatocellular carcinoma (HCC)]. One patient who relapsed was diagnosed with recurrent metastatic HCC.

Most patients were treated with tacrolimus-based immunosuppressive therapy. Dose adjustments of immunosuppressants were made in 26% and 7% of patients during and after the completion of antiviral treatment, respectively. Dose reductions of immunosuppression were significantly more frequent in patients with early fibrosis versus those with advanced fibrosis; no patient with early fibrosis required augmentation of immunosuppression (see Table 5). On the other hand, patients with advanced fibrosis were more likely to require an

increase in their tacrolimus dose because of low levels with no associated elevation of liver chemistries (P 5 0.007). Few patients were treated with different regimens containing cyclosporine3 or the inhibitors of mammalian target of rapamycin (mTOR) sirolimus[7] and everolimus[1]; mycophenolate mofetil (MMF) was often used as an adjunct to other agents, but no patients required dose adjustments of this agent. No significant changes in the plasma levels of sirolimus or cyclosporine were noted in LT recipients who used these agents for immunosuppression, and consequently, no dose adjustments of the immunosuppression were made in these groups. Importantly, no significant biochemical abnormalities or hepatic decompensation were noted in LT recipients treated with sirolimus or cyclosporine.

DISCUSSION

The combination regimen of sofosbuvir and simeprevir, also known as the COSMOS (Combination Of Simeprevir and sOfosbuvir in HCV genotype 1 infected patientS) regimen from its pivotal phase 2 trial, was the first all-oral interferon-free regimen to be used in clinical practice with an efficacy (SVR12) more than 90% for HCV genotype 1 infection in the non-LT setting.[19] The addition of ribavirin to sofosbuvir and simeprevir did not improve SVR12 but, as expected, resulted in a marked increase of AEs such as hemolytic anemia and skin rash.[19] On the basis of the results from the COSMOS trial, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America updated the treatment guidelines in January of 2014 and endorsed the efficacy of 12 weeks of this regimen in non-LT populations with HCV genotype 1 infection, regardless of the stage of fibrosis.[20] The FDA, however, did not approve this regimen until November 2014, and the approval was made with a specific change in the duration of therapy for individuals with cirrhosis (treatment-na€ıve or treatment-experienced), recommending 24 weeks of therapy in this population.[21] Data from the COSMOS trial showed that the proportion of individuals achieving SVR12 was, although numerically higher in the group treated for 24 weeks versus 12 weeks (86% versus 100%), not statistically significant.[19]

At the present time, the only FDA-approved antiviral regimen for the treatment of recurrent HCV genotype 1 infection in LT recipients (including compensated cirrhosis) is ritonavir-boosted paritaprevir, ombitasvir, dasabuvir, and ribavirin for 24 weeks. The AASLD guidelines also endorse the combination of sofosbuvir, ledipasvir, and ribavirin for 12 weeks or sofosbuvir in combination with ledipasvir for 24 weeks for LT recipients with compensated liver disease who are intolerant of ribavirin.[17]

The results from our study demonstrate that a 12-week regimen of sofosbuvir and simeprevir was well tolerated and achieved SVR12 in 93.4% of LT recipients with recurrent HCV genotype 1 infection; this is comparable to non-LT populations.[19] LT recipients with genotype 1b had a 100% SVR12 rate, regardless of the stage of fibrosis; on the other hand, a diminished SVR12 rate was noted for LT recipients with genotype 1a who had advanced fibrosis or cirrhosis (67%). These results are in concordance with data presented from other transplant centers at the AASLD Liver Meeting in November 2014,[22] which are referenced by current AASLD guidelines endorsing the use of the combination of sofosbuvir and simeprevir with or without ribavirin in LT recipients with HCV genotype 1 infections. Our study demonstrates high SVR rates in LT recipients treated with a ribavirin-free regimen.

Importantly, this regimen was highly effective (100% SVR) in treating HCV subtype 1b, regardless of the stage of fibrosis, and subtype 1a when advanced fibrosis/cirrhosis was absent. We did observe suboptimal efficacy of sofosbuvir and simeprevir in LT recipients with HCV subtype 1a and advanced fibrosis/ cirrhosis of the allograft. The role of the concomitant use of ribavirin in this specific subgroup and its impact on SVR remain unstudied and should be an area for future research.

The deleterious effects of recurrent HCV infection in LT recipients include increased overall morbidity, rapid progression of fibrosis, a higher incidence of HCC, an increased need for retransplantation, and diminished patient and allograft survival.[3,23-26] A growing body of evidence confirms that SVR is associated with improved outcomes in non-LT individuals, including reductions in overall morbidity, a decreased incidence of hepatic decompensation and HCC, and regression of hepatic fibrosis.[4,27-30] Data confirming improvements of fibrosis in LT recipients successfully treated with antiviral therapy by sequential histological assessments or by transient elastography are needed.

Previous treatment failure with antiviral regimens containing older generation protease inhibitors such as boceprevir and telaprevir has been proposed as a predictor for treatment failure with the new generation of protease inhibitors such as simeprevir. The main concern is the presence of the naturally occurring Gln80Lys (Q80K) polymorphism, which results in diminished efficacy of simeprevir when it is used in combination with pegylated interferon and ribavirin.[17] However, when simeprevir is used in combination with sofosbuvir, the clinical significance of this polymorphism is markedly attenuated or even eliminated because data from the COSMOS trial suggested that there was no significant difference in SVR between individuals with and without the Q80K polymorphism.[19] The number of patients in our study who had previously been treated with boceprevir or telaprevir was small (8%); therefore, we could not evaluate the impact of prior exposure to protease inhibitors on treatment outcomes.

Combination therapy with sofosbuvir and simeprevir proved to be safe and well tolerated in non-LT populations, with the incidence of severe AEs being extremely low (0%-3%) in the absence of concurrent use of ribavirin.[19] Our results demonstrate that this regimen was also well tolerated in LT recipients (including those with advanced fibrosis or cirrhosis), with no severe AEs recorded and the majority of AEs being fatigue, headache, and nausea. Hyperbilirubinemia, an AE related to simeprevir, occurred only in 2 patients and did not require an interruption of therapy.

Finally, drug-drug interactions are an area of major concern in LT recipients because multiple agents may interact with the metabolism of commonly used immunosuppressants and can result either in increased serum levels that may be associated with toxicity or in diminished serum levels that may jeopardize graft survival. Sofosbuvir does not interact with immunosuppressive agents commonly used in LT recipients; however, simeprevir may alter the metabolism of tacrolimus and cyclosporine.[31] In our study, dose adjustments of tacrolimus were made in 25% of LT recipients treated with sofosbuvir and simeprevir, with dose reductions being more common than dose escalations. Furthermore, dose reductions of tacrolimus were significantly more common in LT recipients with early fibrosis versus LT

recipients with advanced fibrosis. No significant changes were made to doses of mTOR inhibitors.

This large series of LT recipients treated with a combination of sofosbuvir and simeprevir demonstrates high efficacy and safety for this regimen. A major strength of this study is the inclusion of a significant proportion of LT recipients with advanced fibrosis and cirrhosis (38%), a cohort of particular interest in clinical practice that was excluded from a recent trial of ritonavir-boosted paritaprevir, ombitasvir, dasabuvir, and ribavirin.[32] Limitations of our study include its retrospective nature, and the lack of availability of Q80K polymorphisms for individuals who had post-treatment virological relapse. The frequency of AEs could have been underestimated, despite protocolized efforts to record them. We had only a small proportion of LT recipients using cyclosporine for immunosuppression (5%), and this precludes the formulation of any conclusions about clinically significant drug-drug interactions between this agent and simeprevir. Antiviral therapy was administered for a 12-week duration, regardless of the stage of fibrosis, because before November 5, 2014, there had been no previous official guidance by the FDA on the length of treatment with this combination regimen. The impact of a longer duration of therapy on LT recipients, particularly those with cirrhosis and HCV genotype 1a, will be an area of great interest for practicing clinicians. Our study did not evaluate changes in fibrosis after SVR; it will be important for future research to demonstrate this with either histology or noninvasive methods such as transient elastography. Long-term outcomes after successful antiviral therapy with direct-acting antivirals in LT recipients are also an area for future research.

In conclusion, treatment with a 12-week course of sofosbuvir and simeprevir resulted in a 93.4% SVR rate among LT recipients with a recurrent HCV genotype 1 infection: a 100% SVR rate for genotype 1b (regardless of the stage of fibrosis) and an 89% rate for genotype 1a (100% in METAVIR F1-F2 and 67% in METAVIR F3-F4). Furthermore, treatment with this regimen was well tolerated and resulted in no severe AEs. The high efficacy and excellent tolerability of this all-oral, interferon/ribavirin-free regimen in a cohort of LT recipients with several characteristics that were historically considered predictors of poor treatment outcomes such as immunosuppression, prior treatment experience, advanced fibrosis, and even decompensated cirrhosis are very encouraging. Data evaluating a longer duration (24 weeks) of treatment for LT recipients with HCV genotype 1a and advanced fibrosis (METAVIR F3-F4) as well as long-term outcomes of successful antiviral therapy for patient and allograft survival are needed.

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Abbreviations:

AASLD	American Association for the Study of Liver Diseases
AE	adverse event
BMI	body mass index

CI	confidence interval
EOT	end of treatment
FDA	US Food and Drug Administration
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
IQR	interquartile range
LT	liver transplantation
MMF	mycophenolate mofetil
mTOR	mammalian target of rapamycin
RVR	rapid virological response
SVR	sustained virological response
SVR12	sustained virological response at 12 weeks

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TABLE 1.

Demographic and Clinical Characteristics at Baseline

Characteristic	Overall Subjects (n 5 61)	Genotype 1a (n 5 35)	Genotype 1b (n 5 26)	*P* Value
Male sex	32 (52)	20 (57)	12 (47)	0.39
Age, years	61 (58-65)	61 (58-64)	62.5 (57-67)	0.24
BMI, kg/m^2	28 (25-33)	28 (25-33)	28 (26-31)	0.62
Race				
White	31 (51)	20 (57)	11 (42)	0.26
Hispanic and Latino	23 (37)	10 (29)	13 (50)	
Black and African American	7 (11)	5 (14)	2 (8)	
Time after LT, years	5.4 (1.9-8.4)	3.7 (1.6-9.4)	6.3 (3-8)	0.93
Kidney transplant	3 (6)	2 (5.7)	1 (4)	>0.99
Baseline HCV RNA, IU/mL	2,722,473 (656,500-5,436,036)	3,498,287 (954,960-7,473,198)	1,602,793 (542,988-4,097,443)	0.18
HCV genotype 1a	35 (57)	—	—	—
HCV genotype 1b	26 (43)	—	—	—
Nonresponder or relapse to prior treatment	42 (69)	24 (69)	18 (69)	>0.99
Prior treatment stopped because of AEs	13 (21)	7 (20)	6 (23)	>0.99
Protease inhibitor–experienced	5 (8)	3 (8)	2 (8)	0.90
METAVIR F0-F2	38 (62)	23 (66)	15 (58)	0.59
METAVIR F3-F4	23 (38)	12 (34)	11 (42)	
Hepatic decompensation	8 (13)	3 (9)	5 (19)	0.27

NOTE: Data are given as n (%) or median (IQR). Parametric or nonparametric (2 tailed Chi-square) analyses were performed as appropriate.

TABLE 2.

Virological Response According to HCV Genotype 1 Subtypes

	Genotype 1a			Genotype 1b		
	METAVIR F0-F2 (n 5 23)	METAVIR F3-F4 (n 5 12)	*P* Value	METAVIR F0-F2 (n 5 15)	METAVIR F3-F4 (n 5 11)	*P* Value
RVR	19 (83)	4 (33)	0.007 *	11 (73)	7 (64)	0.68 *
Week 8	22 (96)	12 (100)	—	14 (93)	10 (91)	—
EOT	23 (100)	12 (100)	—	15 (100)	11 (100)	—
SVR12 [95% CI]	23 (100) [88-100]	8 (67) [39-86]	0.01 *	15 (100) [79-100]	11 (100) [74-100]	—

NOTE: The 95% CIs are shown for SVR12.

* Fisher's exact test.

TABLE 3.

Comparison of Patients With Genotype 1a Infection Who Achieved SVR12 and Those Who Relapsed

Characteristic	SVR12 (n 5 8)	Relapse (n 5 4)	*P* Value
Male sex	5 (62.5)	4 (100)	0.49
Age, years	58.5 (53-67)	59.5 (58-62.5)	0.95
BMI, kg/m^2	27 (25-32)	25 (23-28)	0.40
Race			
White	3 (37.5)	3 (75)	0.37
Hispanic and Latino	4 (50)	1 (25)	
Black and African American	1 (12.5)	0	
Time after LT, years	4.5 (1.4-7.8)	9.2 (1.9-15)	0.38
Baseline HCV RNA, IU/mL	3,723,569 (529,577-15,762,688)	4,486,950 (1,319,189-17,478,830)	0.90
Nonresponder or relapse to prior treatment	8 (100)	3 (75)	0.33
Protease inhibitor–experienced	2 (25)	1 (25)	>0.99
Cyclosporine or sirolimus use	0	3 (75)	0.02*
Presence of varices	0	2 (50)	0.09
Hepatic decompensation	1 (12.5)	2 (50)	0.23

NOTE: Data given as n (%) or median (IQR). No patients had a history of renal transplant in either group. Two patients in the relapse group died after SVR12.

*Fisher's exact test.

TABLE 4.

Safety Outcomes for Patients Comparing AEs in Individuals With METAVIR F0-F2 Versus F3-F4

AEs	METAVIR F0-F2 (n 5 38)	METAVIR F3-F4 (n 5 23)	*P* Value*	Total (n 5 61)
Any AE	22 (58)	12 (52)	0.79	34 (56)
Grade 3 or 4 AE	2 (5.3)	4 (17.4)	0.18	6 (9.8)
Death†	0	0	—	—
Hepatic decompensation	0	2 (8.7)	0.13	2 (3.3)
Interruption of therapy	0	1 (4.3)‡	0.37	1 (1.6)
Emergency department visit or hospital admission	2 (5.3)	4 (17.4)	0.12	6 (9.8)
Rash	5 (13)	2 (8.7)	0.70	7 (11.5)
Photosensitivity	5 (13)	3 (13)	—	8 (13)
Fatigue	13 (34.2)	4 (17.4)	0.23	17 (27.9)
Headache	8 (21)	3 (13)	0.51	11 (18)
Nausea	3 (7.9)	3 (13)	0.66	6 (9.8)
Increase in bilirubin (>1 mg/dL)	1 (2.6)	1 (4.3)	—	2 (3.3)
Increase in creatinine (>0.5 mg/dL)	3 (7.9)	2 (8.7)	—	5 (8.2)
Anemia (decrease in hemoglobin <10 g/dL)	1 (2.6)	1 (4.3)	—	2 (3.3)
Infection	1 (2.6)	1 (4.3)	—	2 (3.3)

*Fisher's exact test.

†Two patients died after SVR12 (not related to therapy).

‡Interruption of therapy not related to AEs from antiviral agents.

TABLE 5.

Baseline Immunosuppression and Changes While on Therapy

	METAVIR F0-F2 (n 5 38)	METAVIR F3-F4 (n 5 23)	*P* Value
Tacrolimus monotherapy	23 (60.5)	14 (60.9)	—
Tacrolimus/MMF	9 (23.7)	5 (21.7)	—
Tacrolimus dose reduction	11 (28.9)	1 (4.3)	0.007
Tacrolimus dose increased	0	3 (13)	
Cyclosporine/MMF	2 (5.3)	1 (4.3)	—
mTOR monotherapy	2 (5.3)	1 (4.3)	—
mTOR/MMF	2 (5.3)	2 (8.7)	—
mTOR dose reduction	1 (2.6)	0	—

NOTE: Data are given as n (%).