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Sofosbuvir plus Simeprevir Treatment of Recurrent Genotype 1 Hepatitis C after Liver Transplant

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4)Abstract

Patients with recurrent hepatitis C (HCV) infection post liver-transplant can be difficult to treat safely and effectively. A prior (COSMOS) study in non-transplant HCV patients, using sofosbuvir plus simeprevir, had high efficacy and tolerability in treating HCV genotype 1 patients, even prior non-responders to interferon therapy and those with cirrhosis. Our aim was to evaluate the efficacy of sofosbuvir and simeprevir in genotype 1 HCV post-liver transplant patients.

In this prospective, observational study, patients received sofosbuvir 400mg plus simeprevir 150mg daily for 12 weeks without ribavirin. The primary endpoint was a sustained virologic response 12 weeks after the end of therapy.

Forty-two patients completed treatment. Twenty-six percent started treatment <6 months post-liver transplant. Nineteen percent of the included patients had cirrhosis, 14% with decompensation. At week 4 on treatment, 21% of patients had detectable virus but at the end of treatment, 100% were undetectable. Twelve weeks after the end of treatment, 95% of patients had undetectable hepatitis C. The regimen was generally well tolerated.

Conclusion: The oral regimen of sofosbuvir plus simeprevir without ribavirin is efficacious and well tolerated in the treatment of genotype 1 hepatitis C patients post-liver transplant.

5) Key Words: liver transplant, hepatitis C, direct acting anti-viral agents, sofosbuvir, simeprevir

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Introduction: Hepatitis C (HCV) is a leading cause of liver transplantation (LT) in the United States (1) and carries a worse prognosis after transplant compared to several other underlying causes of liver disease (2). Persistence of HCV viremia after LT is essentially universal. A chronic hepatitis develops in 62-80% of patients, cirrhosis recurs in 30% within 5 years (3,4), and 20% require repeat LT (5,6). Up to 9% of LT for HCV develop an aggressive post transplant course, fibrosing cholestatic hepatitis, with a high mortality (7). HCV eradication post-LT improves fibrosis and patient survival (1). Given their often complex medical regimens, susceptibility to graft rejection, anemia, marrow suppression and frequent renal insufficiency (RI), post LT HCV patients can be difficult to treat with conventional interferon/ribavirin-based regimens. RI is common after LT. A serum creatinine >1.6 mg/dL is found in >75% of LT recipients after >3 years of follow up. Given all of the above factors, there is some urgency in finding safe and effective regimens for HCV eradication soon post-LT including in the presence of RI. Recently, in non-transplant patients, regimens including sofosbuvir (Sovaldi, Gilead, Foster City, CA), an NS5B nucleotide polymerase inhibitor, have produced a sustained virological response (SVR) close to 100% in the treatment of HCV without the need for pegylated-interferon (8-11). Results from the COSMOS study (12) demonstrated high efficacy and good tolerability in the treatment of HCV genotype 1 patients using sofosbuvir in

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combination with the NS3 protease inhibitor simeprevir (Olysio, Janssen, Titusville, NJ) with and without ribavirin. The cohort with cirrhosis included prior null responders and achieved an SVR12 of 94%.. The outcome of HCV treatment with sofosbuvir and simeprevir without ribavirin in post-liver transplant patients is unclear. The aim of our prospective, observational study was to evaluate at a single center the safety and efficacy of sofosbuvir plus simeprevir for genotype 1 HCV patients post LT, including those recently transplanted, with renal insufficiency, and with cirrhosis including decompensation.

Methods

Study Design and Population. This was a prospective, observational single center study. The study protocol (H-4804) was approved by the Institutional Review Board at the University of Massachusetts Medical Center. Adult patients were included in the study if they had a living or deceased donor LT for genotype 1 HCV cirrhosis between 2002-2014 and had recurrent HCV. Other inclusion criteria included patients who were naïve to HCV treatment, had partial response to or relapse after prior interferon-based treatment pre- or post-LT, had compensated or decompensated cirrhosis, and those with chronic renal insufficiency even on hemodialysis. The first forty four consecutive patients who were newly transplanted or encountered in the liver transplant clinic during routine follow-up were enrolled in the study. Exclusion criteria included active malignancy, infection with HIV, chronic hepatitis B, and active alcohol or substance abuse. Patients were also excluded if their health insurance denied coverage of the medications. None of the initial forty four patients met exclusion critera and therefore all were included in the study. Genotype and viral titers were verified prior to the initiation of therapy.

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Forty four patients were offered treatment. All were initially included and treated with the oral regimen of sofosbuvir 400mg and simeprevir 150mg daily for 12 weeks without ribavirin. Two patients were excluded from analysis. One (2.3%) of these patients stopped the medications after 2 weeks because of "flu-like" symptoms that persisted after discontinuation, and another patient did not return for follow up after 8 weeks on therapy. Forty two patients (95.5%) reached end of treatment (EOT) and were included in the study for analysis.

Definition and ascertainment of outcome. "Undetectable" HCV PCR Quantitative (Quant) test was defined as viral load <15 IU/mL (COBAS AmpliPrep Taqman HCV test version 2, limit of detection 15 IU/ml) and was assessed at the end of week 4 of treatment (rapid virologic response or RVR). This viral load detection level is under the detection level of 25 IU/mL recommended by the AASLD guidelines for the assessment of viral response. Patients achieving an RVR received a standard total 12 week treatment course (EOT). For those not achieving an RVR, the HCV Quant was checked weekly until negative. These patients then received additional medications to receive 8 weeks of therapy after they achieved an undetectable HCV to get a true "EOT" sample. For those not achieving RVR, treatment duration was therefore extended an additional 2-4 weeks. The HCV titer was then checked at 4, 12, and 24 weeks after finishing therapy to determine the SVR4, SVR12, SVR24 response rates respectively. The major efficacy endpoint was the percentage of patients with undetectable HCV PCR 12 weeks after the end of treatment. Additional efficacy end-points were rates of undetectable HCV at week 4 on treatment, at EOT, SVR4 and for those patients out far enough, SVR24.

Monitoring for adverse events and immunosuppression changes. Patients were followed regularly in the LT clinic by the transplant pharmacist, hepatologists, and nurse coordinators. New symptoms or adverse events which developed during treatment were considered possibly

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attributable to the DAAs. Adjustments to immunosuppressive medication doses were made as judged clinically necessary. Immunosuppression levels, complete blood counts, and comprehensive metabolic panels were obtained 1 and 4 weeks after starting sofosbuvir and simeprevir, and shortly after the end of treatment. Patients treated after a recent LT had more frequent laboratory checks as per post LT protocol.

Results

Patient Characteristics. Forty-two GT1 HCV post-LT patients started treatment between December 13, 2013 and September 30, 2014 and had data available at the end of therapy, EOT. All except 2 were transplanted at this center. Between 2002-2014, 423 deceased or living donor liver transplants were performed at UMass Memorial Center. Thirty-nine percent (164) of the LTs were done for HCV related cirrhosis, and 71% (117) of the patients transplanted for HCV had genotype 1a or 1b. Recurrent HCV was universal after transplant. Sixty-four percent (75) of the post LT genotype 1 HCV patients were still alive at the start of the study. The first consecutive eligible 44 patients (59%) were offered treatment with sofosbuvir and simeprevir and were included in the study. A few remaining post LT genotype 1 HCV patients were treated with sofosbuvir and simeprevir but not included in the study because they had not completed treatment by the submission of this manuscript.

The patient characteristics are shown in **Table 1**. Median time interval between LT and initiation of sofosbuvir and simeprevir was 28 months, and 26% (11 patients) started treatment six months or less after LT. At the start of treatment, 19% (8 patients) had advanced fibrosis diagnosed by either a liver biopsy with at least 5/6 fibrosis (Ishak) or imaging demonstrating cirrhosis and portal hypertension. The mean MELD score in this group was 12. Fourteen percent

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(6 patients) had decompensation with either ascites or variceal bleed. Seventeen percent (7 patients) were listed or evaluated for re-transplantation. One patient (2.4%) underwent re-transplant 4 months after living donor liver transplant and continued treatment during re-transplant. Another patient (2.4%) was re-transplanted <1 month after achieving SVR12.

Treatment response, RVR and SVR. All forty-two patients completed treatment and are at least 12 weeks post-treatment. Seventy-nine percent (33 patients) had no detectable virus at week 4, while 21% (9 patients) did not achieve an RVR. All 42 patients reached EOT and had undetectable HCV. Forty of 42 (95%) were undetectable for SVR 4 and SVR12. One patient (2.4%) relapsed within 4 weeks and another patient (2.4%) had an undetectable viral load at EOT but has not returned to obtain blood work for SVR 4 or 12 (see **Figure 1**). The patient who relapsed has cirrhosis and the other patient who did not return for blood work did not have evidence of advanced fibrosis (see **Figure 2**). Of the 8 patients with known advanced fibrosis, 87.5% achieved SVR 12. Of the remaining 34 patients without known advanced fibrosis, 97% achieved SVR 12. The difference in the SVR 12 rate between the two groups was not statistically significant (p=0.10 chi squared test).

Patients not attaining RVR. Twenty-one percent (9 patients) had a detectable HCV PCR Quant at week four of treatment. Their treatment course was individualized and extended to 8 weeks beyond the date that their viral load became undetectable. Their total duration of treatment was therefore 14-16 weeks (mean 15 weeks). Of the nine patients who did not clear HCV by 4 weeks of therapy, 56% (5) were within one year of LT. The remaining 44% (4 patients) were at least 2 years post-LT. Of the 9 patients who had detectable HCV PCR at week 4 of treatment, 33% (3 patients) had been unsuccessfully treated with interferon based regimens in the past. None of the patients had cirrhosis. The median starting HCV titer of those 9 patients detectable

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at wk4 (1.49 million IU/mL, range 0.10 – 82.5 million IU/mL) was similar to those 33 achieving RVR (1.77 million IU/mL, range 0.03 – 32.3 million IU/mL).

Changes to Immunosuppression

The majority of patients (88%) were on tacrolimus-based immunosuppression, 7.1% (3 patients) were on cyclosporine, and 4.8% (2 patients) on rapamune based therapy. During HCV treatment, 26.2% (11 patients) required tacrolimus dose changes. Of the patients requiring tacrolimus dose changes, 55% were within a year of LT. Sixty-four percent of the patients requiring tacrolimus dose changes required a decrease in their immunosuppression dose. The remaining 36% required several minor changes to their tacrolimus dose. After completing the sofosbuvir and simeprevir medications, 12% (5 patients) required readjustment of their tacrolimus dose. Eighty percent of these changes were an increase to the tacrolimus dose. Overall, adjustments to the tacrolimus doses were similar to the usual practices in post-LT patients. None of the patients on rapamune or cyclosporine required changes to their immunosuppression doses.

Safety and tolerability

Most patients (74%) tolerated the DAAs well with minimal side-effects (see **table 2).** During treatment, 33% (14 patients) had adverse effects including confusion, transient increase in aminotransferases, pneumonia, edema, fatigue, fever, rash, shingles, joint pain, clostridium difficile infection, bacteremia, and pulmonary embolus (PE). The PE occurred in one patient who was less than 1 month post LT. However, it is unknown if the symptoms and adverse events were related to the sofosbuvir and simeprevir. The most common side-effect was a mild transient rash in 12% (5 patients). None of the patients required dose reduction or discontinuation of the

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sofosbuvir or simeprevir. No patients experienced acute cellular or humoral rejection. One death occurred 4 months after finishing a full treatment course and was thought not to be related to the HCV medications.

Patients were followed for changes in renal function. Sixty-nine percent (29 patients) had an initial GFR <60, 1 of whom (2.4%) was on hemodialysis. The GFR was unchanged (GFR ≤5 mL/min difference between start and end of treatment) in 69% (29 patients), improved in 21% (9 patients) and declined in 10% (4 patients). After the completion of the sofosbuvir and simeprevir medications, 5% of patients sustained a decreased GFR.

Discussion:

There is limited published data on this difficult to treat post liver transplant HCV population using DAAs without ribavirin (11), and the subject is an area of intense interest. This prospective, observational study at a single center on genotype 1 HCV patients after liver transplant treated with sofosbuvir and simeprevir, an oral only regimen, demonstrates firstly that successful outcomes can be achieved without ribavirin. Results from the COSMOS trial (12) were sufficiently promising for non-transplant patients to justify our approach trying to avoid ribavirin in this population prone to anemia and renal insufficiency. Our results demonstrate that the combination of these two DAAs appears to be effective in achieving SVR in genotype 1 HCV post-LT patients with a high degree of success and was generally well tolerated even in patients with chronic renal insufficiency, decompensated cirrhosis, and with treatment initiated even less than 2 months post-LT.

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In the past, treatment with standard antiviral therapy for HCV, pegylated interferon and ribavirin, resulted in an undetectable viral load in only 18-45% of treated post-transplant patients with HCV, and was less likely in patients with cirrhosis and genotype 1 (1,13-15). The side effects of the standard interferon based treatment, including anemia, decompensation of cirrhosis, and interactions with immunosuppressive agents, are generally not well tolerated by post-LT patients (1,13,14). Dose reduction with peg-interferon and ribavirin was necessary in 70% of patients (1,13,14). Treatment with the protease inhibitors boceprevir and telaprevir, gave a 63% SVR12 (18) however, still required interferon and ribavirin and were not well tolerated by post-transplant patients. In prior studies with these medications, 43% of patients discontinued treatment due to failure or adverse events, 27% were hospitalized, and 9% died (18). Drug-drug interactions also make treatment of this patient group challenging (19). Our results represent a significant improvement in the treatment of LT patients with GT1 HCV.

In our study of 42 patients, 79% achieved RVR and 95% have achieved SVR12. Viral and/or host factors may explain why 21% of patients did not achieve RVR and 5% did not achieve SVR 12. Neither noncompliance, time from LT, prior treatment attempts with IFN-based regimens, renal insufficiency, nor HCV titer at the start of treatment appeared to be a factor. The difference in SVR 12 rates of patients with and without advanced fibrosis was not statistically significant however the number of patients with cirrhosis in our study was small.

As of the time of this publication, 95% (38/40) patients who have reached 24 weeks after the completion of treatment have undetectable HCV (SVR24). We were optimistic that those remaining patients with an SVR12 would extend to a full SVR24, the conventional definition in the IFN era of 99.9% likelihood of eradication for at least 5 years (20). At least in pre LT populations, it is emerging that a SVR4 in patients treated with sofosbuvir containing regimens is

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highly likely (98%) to translate to an SVR12 and "cure" (21,22). When relapses have been observed after the use of DAA agents, they have generally been rapid (9,23,24). In prior studies, 77% of the relapses were within 4 weeks of treatment (21), and "none" relapsed beyond 12 weeks after stopping (22). Thus, it is quite possible that even an SVR4 will predict an overall high likelihood of ultimate SVR. To date, in our limited study, we have not yet seen any relapses if patients achieved an SVR4 using our protocol, but caution is necessary because these are post-LT patients, and the estimates of durability of SVR4 were based on pre LT patients.

We did not discontinue treatment in those patients detectable at 4 week. Instead, we employed an individualized strategy of extending the length of treatment to achieve an 8 week duration of undetectable virus. This strategy may have altered a potential 79% success rate to our observed 95% SVR4. The kinetics of the disappearance of HCV in the serum has been quite variable and slower viral loss in post LT patients has been suggested and might contribute to a lower SVR4 response (25). To better define the optimal duration of treatment in those who do not achieve RVR, further randomized, prospective studies are necessary. Another preliminary study noted 46% RVR and 37% EOT rates in post-LT patients treated with sofosbuvir and simeprevir (26). Our extension approach in patients who have detectable HCV at week 4 may have contributed to our improved outcomes.

Simeprevir does have the potential for interaction with immunosupressive medications (27). Almost 90% of our patients were managed with tacrolimus based immunosuppression. Sofosbuvir and simeprevir seem to be safe even in recently transplanted patients who may require many changes in medications and immunosuppression doses and are also vulnerable to the side effects of these medications. There did not appear to be a consistent pattern of required alteration in immunosuppression. There has been some concern with the use of cyclosporine and

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DAAs (27), but we did not observe significant problems in our few patients on cyclosporine. There were no episodes of clinical rejection during or after the HCV treatment in any of our patients.

The combination of sofosbuvir and simeprevir was overall well tolerated. Side effects were typically minimal. Hyperbilirubinemia has been reported as a side effect of sofosbuvir but in our review, the 7% (3 patients) who had changes in their liver function tests only had an increase in their aminotransferases. All three patients were within 3 months of LT. Their AST/ALT transiently increased to 10-25x the upper limit of normal and normalized despite continuation of the DAAs. Major adverse events in 5% (pulmonary embolism and bacteremia in one patient each) were not clearly related to the DAAs.

There are at least theoretical concerns in using sofosbuvir in RI since the main metabolite GS-331007 is renally excreted and accumulates in RI (28). There was no consistent decline in renal function on treatment. During treatment with sofosbuvir and simeprevir, more patients (21%) improved than declined in a sustained manner (5%), and one recently transplanted patient came off hemodialysis.

Our data supports favorable EOT, SVR4, and SVR12 responses with sofosbuvir and simeprevir in the post-LT treatment of genotype 1 HCV patients.

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Author's contributions:

All authors provided substantial contributions to the conception and design of the study, acquisition of the data, and drafting or revising the paper. All authors have approved of the final article.

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Table 1

Patient characteristics at the initiation of HCV treatment with sofosbuvir and simeprevir

Characteristics		**Total Number**	**Percent of Total Patients**
Mean age in years		58	
Sex			
	Female	14	33%
	Male	28	67%
EthnicityEthnicity			
	Caucasian (nonHispanic)(nonHispanic)	34	81%
	Black (nonHispanic)(nonHispanic)	1	2%
	Asian	1	2%
	Hispanic	6	14%
Genotype 1a		33	79%
Genotype 1b		8	19%
Genotype 1 unknown		1	2%
Advanced Fibrosis (stage 5-6/6)Advanced Fibrosis		8	19%
Time from transplant			

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	< 2 months	5	12%
	2-6 months	6	14%
	7-12 months	4	10%
	>12 months	27	64%
Type of Transplant	Deceased donor	37	88
	Living donor	5	12%
Immunosuppression			
	Tacrolimus	37	88%
	Cyclosporine	3	7%
	Rapamune	2	5%
Renal Insufficiency (GFR <60)		29	69%
Hemodialysis		1	2%
Prior HCV Treatment		20	48%
	Pre-Transplant	11	26%
	Post-Transplant	9	21%

Table 1.: Patient characteristics at the beginning of treatment with sofosbuvir + simeprevir. Demographics, genotype 1a or 1b, time from transplant, renal function, immunosuppression, and prior HCV treatment are included. Patients with advanced fibrosis were either documented by a liver biopsy with stage 5-6/6 fibrosis or evidence of cirrhosis and portal hypertension on imaging within the year prior to treatment.

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Table 2.

Reported adverse events and side effects while on treatment

Side effects and adverse events	Number of Patients	Percentage of Total Patients
Aminotransferase increase	3	7.1%
Confusion	1	2.4%
Pulmonary embolism	1	2.4%
Clostridium difficile	1	2.4%
Rash	5	12%
Fatigue	1	2.4%
Shingles	1	2.4%
Pneumonia	1	2.4%
Edema	1	2.4%
Joint pain	1	2.4%

Only 33% (14 patients) reports side effects or adverse events while on sofosbuvir and simeprevir. Some patients reported multiple symptoms.

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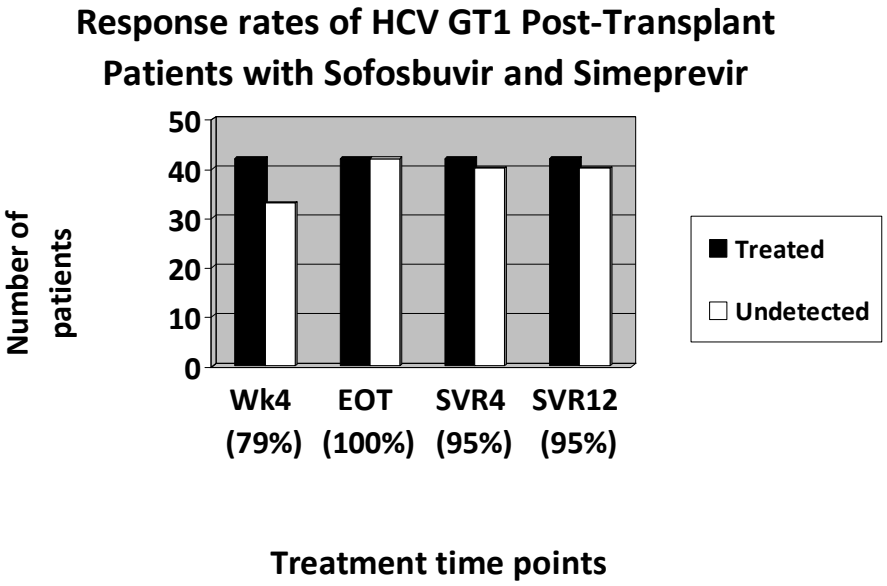
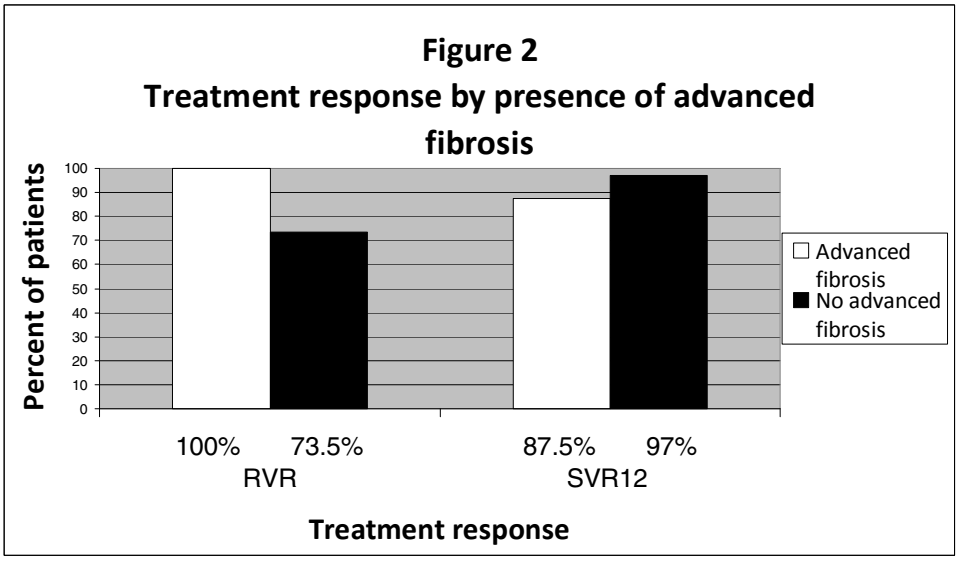
Figure 1





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