Sofosbuvir and Ribavirin for 24 Weeks Is An Effective Treatment Option for Recurrent Hepatitis C Infection After Living Donor Liver Transplantation

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Background: Recurrent hepatitis C virus (HCV) has been a serious problem after liver transplantation (LT). We report our experience of 24-week therapy with sofosbuvir (SOF) and ribavirin (RBV) in post-LT recurrent HCV in living donor liver transplantation (LDLT) setting in South Asia. **Methods:** Data from all patients treated for post-transplantation HCV recurrence in a single center were analyzed. Treatment regimen was 24 weeks of SOF 400 mg daily and RBV (starting at 800 mg daily, increased as tolerated). Sustained virological response (SVR) was assessed 12 weeks and 24 weeks after completion of treatment. **Results:** 63 patients (median age 52 [range 30–69] years; 80% males) were treated. Most (76.2%) were treatment experienced and predominant HCV genotype was 3 (77.7%) followed by 1 (20.6%). Median transient elastography (Fibroscan) score was 7 (range 3–11) kPa and none of the patients had cirrhosis. SVR12 was achieved in 60 of 63 patients (95.2%) while SVR24 was noted in 59 (93.7%). SVR12 rates were as good in genotype-3 as in genotype-1. Older age, longer period after transplantation, higher Fibroscan value and higher need for erythropoietin were likely to be associated with relapse. Adverse effects were noted in 34 patients and weakness and fatigue were the commonest side effects. Significant drop in hemoglobin (<8 g/dL) was seen in 6 patients. **Conclusions:** SOF + RBV combination therapy for 24 weeks was safe and effective in treatment of for post-LT recurrent HCV in a single LT center and remains relevant due to its low cost and lack of drug interactions. (J CLIN EXP HEPATOL 2017;7:165–171)

Recurrent hepatitis C virus (HCV) infection is common after liver transplantation (LT) for HCV related cirrhosis and may be seen in over 80% such cases.^{1,2} It can lead to graft loss due to rapid development of cirrhosis³ in 20–40% patients or less often due to fibrosing cholestatic hepatitis in 2–5%. It is also a recognized cause of mortality in these patients. Achievement of sustained viral response (SVR) with treatment can improve outcome significantly in these patients,⁴ but use of interferon containing regimens is associated with significant morbidity.⁵ Therefore it has been considered a difficult to treat group. Availability of directly acting antivirals (DAAs) has shown excellent response rates with interferon free

regimens and it is now possible to treat these patients in post-operative period.^{6–8} In India, the affordable form of new DAAs were made available in a phased manner and accordingly treatment guidelines were evolved to use sofosbuvir (SOF) initially from 01 April 2015⁹ and a combinations of SOF with ledipasvir/daclatasavir subsequently from 15 December 2015.¹⁰ During the period between 01 April and 15 December 2015, all patients with HCV infection at our center, irrespective of genotype, were treated with a combination of SOF and weight based ribavirin (RBV) for 24 weeks. This regimen has been found to be safe and effective for genotypes commonly seen in this part of the world.¹¹ We thus evaluated the efficacy and safety of SOF plus RBV for 24 weeks in patients with recurrent hepatitis C of all genotypes after LT among patients from South Asia.

Keywords: recurrent hepatitis C, living donor liver transplantation, genotype-3, genotype-1, sustained viral response

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Abbreviations: CBC: complete blood counts; DAA: directly acting antivirals; g/dL: grams per decilitre; Hb%: hemoglobin; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; kPa: kilo pascals; KFT: kidney function tests; LFT: liver function tests; LDLT: living donor liver transplantation; LT: liver transplantation; RBV: ribavirin; SOF: sofosbuvir; SVR: sustained virological response

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METHODS

Patients

Patients who had living donor liver transplantation (LDLT) for chronic HCV infection (all genotypes) related cirrhosis and were detected to have recurrent HCV infection after transplantation were subjects for this study. All patients who reported for treatment of recurrent HCV infection between 01 April 2015 and 15 December 2015 were analyzed. Following group of patients were excluded

(a) transplantation for HCC, (b) associated portal vein thrombosis, (c) combined liver-kidney transplantation, (d) those on corticosteroids > 5 mg/day (usually first 3 months after transplantation), (e) human immunodeficiency virus or hepatitis B virus confection, (f) serum creatinine > 2 mg/dL, (g) serum bilirubin > 2.5 mg/dL or evidence of intrahepatic biliary radicals dilatation and (d) concomitant features of cellular rejection or ALT > 3× upper limit of normal (ULN).

Study Design

This study is an analysis of prospectively collected data on patients treated for post-transplant HCV recurrence during the period 01 April to 15 December 2015 at a single center. Patients were treated with SOF 400 mg and RBV (weight based 800–1200 mg) orally every day for 24 weeks. After treatment, patients were followed-up for checking SVR at week 12 and 24 after completion of treatment (SVR12 and SVR24). RBV was started in the dose of 800 mg/day in 2 divided doses. If the hemoglobin (Hb%) level was >12 g/dL after 2 weeks, RBV was increased as tolerated by 200 mg/day at weeks 2, and 4 until the appropriate dose was reached (1000 mg daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight of >75 kg). And if the Hb% was <10 g/dL, the RBV dose was reduced by 200 mg/day and erythropoietin injection starting with 5000 IU subcutaneously was added per week and continued as long as Hb% was <10 g/dL. Erythropoietin dose was increased to 10,000 units and RBV dose further reduced by 200 mg if Hb% did not rise above 10 g/dL. RBV was stopped if hemoglobin remained <8 g/dL despite erythropoietin 10,000 IU per week. Patients were followed up at two-week interval by visits/emails with CBC, LFT and KFT. Many patients in this cohort lived in different countries and it was not practical to strictly follow the timelines noted above. They were advised to be under supervision of their local physician/gastroenterologist and communicate every two weeks by emails. All patients were followed up meticulously and were physically reviewed every six months at our center. Results of Blood tests were monitored locally and entered in proforma as and when emails were received. SVR12 and SVR24 were checked at the time when due or up to 4 weeks later than stipulated time, to be counted as SVR. It was decided to stop treatment if patients developed extensive skin rash not responding to anti-histaminics, ALT levels rose >5× ULN or patient developed other features of graft dysfunction/acute cellular rejection. HCV RNA quantitative assessment was done by using the Roche COBAS TaqMan at following points: pre-treatment, 1 (optional), 6, 9 and 12 months after starting treatment. Drug safety data were collected during treatment and for one-month days after the last dose of study drug. Patients were encouraged to report any fresh symptom they developed. The data on reported adverse events, abnormalities in physical examinations, clinical laboratory

tests, vital signs, and electrocardiogram recordings were tabulated. Adverse events were classified as per conventional criteria.^{12,13} The primary endpoint was achievement of SVR24, defined as HCV RNA below the lower limit of detection (<15 IU/mL) 24 weeks after stopping study drug.

Statistical Analyses

Basic statistics were calculated using Microsoft Excel sheet. Efficacy of drug was expressed as number and percentage of patients who achieved SVR24.

RESULTS

Study Population

A total of 63 patients were treated during the specified period. The baseline parameters in relation to these patients prior to treatment were as summarized in Table 1. Median age of the patients so treated was 52 years (range 30–69 years) and majority (80.9%) were males. Only 4.8% patients had BMI above 30%. Of the 63 patients, 48 (76.2%) were treatment experienced while remaining were naïve. Among the treatment experienced patients, 37 had received a combination of pegylated interferon (Peg-IFN) plus RBV, while 11 has received Peg-IFN monotherapy. All these patients had been treated more than six months prior to their LT. As is common in this subcontinent, majority of patients had genotype-3 infection (49, 76.2%). Genotype-1 was the next common genotype (13, 20.6%), while one patient had genotype-4. Median baseline HCV RNA Levels were 782,372 with a range from 2158 to 18,902,058 IU/mL. Patients had reported for treatment after a median of 11 (range 1–95) months after the transplantation surgery. None of our patients had cirrhosis and the median Fibroscan value was 7 (range 3–11).

One patient was treated for fibrosing cholestatic hepatitis. This was a 46 years old male who was transferred from a neighboring country with progressive increase in jaundice (6 weeks) and development of ascites (15 days) nearly 11 months after his transplantation. His serum bilirubin was 19.8 mg/dL, Serum alkaline phosphatase was 817 and AST/ALT were 210/277 IU. He was diagnosed to have fibrosing cholestatic hepatitis after extensive investigations including a transjugular liver biopsy. He showed dramatic treatment response with gradual improvement of liver functions to near normal over next 17 weeks, disappearance of ascites in 14 weeks and achievement of ETR as well as SVR24. His post-treatment Fibroscan value was 8.4 kPa.

Response to Antiviral Treatment

HCV RNA viral load levels declined rapidly after initiation of treatment, and all patients who were tested ($n = 31$) had reached the level of target not detected (TND) by end of one month's treatment (Table 2). All patient ($n = 63$) were HCV RNA negative at the end of treatment. This included

Table 1 Baseline Demographic Data About the Study Population.

Demography of treatment cohort	N = 63
Age in years, median (range)	52, 30–69
Males, n (%)	51 (80.9%)
BMI > 30% kg/m ²	3/63 (4.8%)
History of prior HCV treatment, n (%)	48 (76.2%)
(a) Pegylated interferon or interferon only, n (%)	11
(b) Peg interferon and RBV, n (%)	37
Response to prior treatment	
(a) HCV RNA positive at end of treatment	32
(b) Unknown	16
HCV RNA viral load before treatment, mean (SD)	2,171,542 (3,311,728.041)
Period after transplantation in months, when reported for treatment in the present study; median (range)	11 (1–95)
Pre treatment HCV RNA viral load, median (range)	782,372 (2158–18,902,058)
Genotype	
1	13 (20.6%)
3	49 (77.7%)
4	1 (1.6%)
Pre-treatment Fibroscan value in kPa, median (range)	7 (3–11)
Pre treatment Hb% in g/dL, median (range)	13 (7–15)
Platelet count, ×103/mL, median (range)	170 (67–440)
Albumin, g/dL, median (range)	3.9 (3.2–5.6)
Total bilirubin, mg/dL, median (range)	0.9 (0.4–2.4)
INR, median (range)	1.1 (0.8–1.4)
ALT, U/L, median (range)	38 (19–88)
Serum creatinine, mg/dL, median (range)	0.8 (0.3–1.4)
TSH, mIU/L	1.3 (0.4–3.7)

Table 2 HCV RNA Quantitative Test Was Done in All Patients Prior to Treatment Followed By At 6 Months (End of Treatment Response), 9 Months (to Check for SVR12) And At 12 Months (to Check for SVR24). By the Time of This Analysis Only 40 Patients Had Completed 12 Months.

Patient characteristics	Pre-treatment	6 months after initiating treatment (ETR)	9 months after initiating treatment (SVR12)	12 months after initiating treatment (SVR24)
Total number studied	63	63	63 ^a	63 ^a
Number of patients with TND	0	63	60 ^a	59 ^a
Percentage of TND	0	100	95.2%	93.7%
HCV RNA levels, mean (SD)	2,171,542 (SD ± 3,311,728.041)	–	3,446,253 (SD±) 397,0216 (among those who were positive)	(One additional patient) 1898

TND: means target not detected (RNA levels below the lower limit of detection).

^aIncludes one patient who had discontinued RBV.

one patient who had discontinued RBV due to side effects after 14 weeks.

Of the 62 patients who completed treatment with SOF and RBV, 60 (96.7%) achieved SVR12. Three patients who had relapsed at 12 weeks after end of treatment, included one patient who had discontinued RBV after 14 weeks and

took SOF monotherapy for remaining period. All the 63 patients included in this study have now completed 24 weeks follow up post-ETR. One patient who had achieved SVR12, was found to be positive for HCV RNA positive when tested 7 months after completing treatment. Virological response by age, sex, BMI, HCV RNA level, HCV

Table 3 Patient Characteristics Among Those Who Responded And Those Who Showed Relapse of HCV After Treatment.

Demography of treatment cohort (n = 63)	SVR24 achieved	SVR24 not achieved	Statistical difference (P value)
Age in years, median (range)	51.1 (6.1)	60 (2.6)	0.005*
Males, n (%)	49/59 (83.1%)	2/4 (50%)	0.3219*
BMI > 30% kg/m ²	24.9288136 (2.96665671)	25.425 (2.86050695)	0.74683823*
History of prior HCV treatment, n (%)	44/59	4/4	0.22648
Period after transplantation in months, median (range)	14.1864407 (15.4467657)	39.5 (39.4334883)	0.006*
(a) <12 months n = 41	40	40	
(b) >12 months n = 22	20	19	0.118
HCV RNA viral load before treatment, mean (SD)	2,246,188.75 (3,393,123.55)	1,070,509 (1,531,787.7)	0.49647376*
Genotype			
1	12/13	1/13	
3	47/49	2/49	0.5129
4	0/1	1/1	
Pre-treatment Fibroscan value in kPa, median (range)	6.42033898 (1.32701112)	8.4 (1.56418243)	0.006*
Pre treatment Hb% in g/dL, mean (SD)	12.7 (1.6)	12.8 (1.2)	0.867
Need for erythropoietin	17/59	3/4	0.09*

*p value.

genotype and Fibroscan values is outlined in Table 3. Number of patients who did not respond was too small for meaningful statistical analysis. However, longer duration after transplant, non-responders to earlier interferon-based therapy and those with higher Fibroscan value seems to confer higher chance of relapse after SOF and RBV in the post-transplantation setting.

Safety

None of the patients developed graft dysfunction during the treatment and there were no deaths. Six patients experienced grade 3 adverse events (severe; or medically significant but not immediately life threatening) and all of them were related to development of anemia, which required additional treatment with erythropoietin and in a few cases even packed cell transfusion. Grade 2 adverse events (moderately severe requiring local or non-invasive intervention) indicated; were more common and grade 1 (mild symptoms; clinical or diagnostic observations only; no intervention indicated) were very common. Total of 77 adverse events were noted in 34 patients. List of grade 2 and 3 adverse events seen is summarized in Table 4. All patients with grade 2 adverse symptoms also had additional grade 1 symptoms. Weakness and fatigue was the commonest side effect noted in 18 patients and all of them had Hb% below 10 g%. Hb < 10 g% was noted in total of 25 patients and 22 of them also received erythropoietin treatment. In 6 patients Hb% had dropped below 8 g%. Erythropoietin was given to 22 patients in dose of 5000 units subcutaneously every week for an average of 9.6 (+5.1) weeks while 8

of these patient required 10,000 units for a duration of 7.7 (3.3) weeks duration in addition to above. On an average need for erythropoietin treatment was noted 5.8 (±4.5) weeks after the onset of treatment. At week 6, the median RBV dose was 600 mg/day, and at weeks 12 through 24, the median dose was 800 mg/day and by end of treatment at week 24, it was again 600 mg/day. No significant change in total leukocyte count, differential leukocyte count was

Table 4 Adverse Events Noted During Treatment With SOF Plus RBV Regimen (Total Number of Patients = 63).

Adverse events shown as n (%)	Grade-1	Grade-2	Grade-3
Weakness, fatigue	11	7	6
Anorexia	9	1	0
Insomnia	2	4	0
Body Aches	7	1	0
Irritability	7	0	0
Headaches	7	0	0
Vomiting	4	0	0
Fever	3	0	0
Itching	3	0	0
Arthralgias	3	0	0
Jaundice	1	0	0
Paresthesia	1	0	0
Number of patients (total adverse events seen)	34 (58)	11 (13)	6 (6)

noted as compared to the baseline. Creatinine levels remained stable during treatment. No significant fluctuation in tacrolimus levels were noted in these patient as the regimen has not been reported to have any interactions with any of the concomitant immunosuppressive agents, which included tacrolimus (all patients), mycophenolate (34 patients), prednisone (5 patients).

DISCUSSION

We have reported 93.7% SVR24 (95.2% SVR12) rates after treatment of post LDLT HCV recurrence with SOF plus RBV for 24 weeks. HCV recurrence was a major problem in the pre-DAA era as treatment with Peg-IFN was associated with poor efficacy, high prevalence of serious adverse effects and risk of rejection.⁵ Currently however treatment regimens with newer DAAs are being recommended as first line treatment for various genotypes. However, in India, the affordable form of new DAAs were made available in a phased manner during 2015 and accordingly treatment guidelines were evolved to use SOF initially from 01 April 2015⁹ and a combinations of SOF with ledipasvir/daclatasvir subsequently from 15 December 2015.¹⁰ During the period between 01 April and 15 December 2015, all patients with HCV infection at our center, irrespective of genotype, were treated with a combination of SOF and weight based RBV for 24 weeks. Analysis of these patients has been presented above.

Patient came for treatment after a mean of 14 months after LDLT and average pre-treatment Fibroscan value was 6.4 kPa. We report SVR12 in 60/63 (95.2%) of patients. SVR24 was a shade lower (93.7%) as one patient (genotype-1) was found to have relapsed by 7 months' post-treatment. Majority of cases seen by us had HCV infection with genotype-3 (49/63 or 77.7%) and only 13 (20.6%) of our patients had genotype-1 infection. SVR12 in genotype-3 was seen in 95.9%. These finding are different from those reported in a multicenter study from the West.⁶ Charlton et al. (2015) reported SVR12 in 70% of their 40 cases studied. In their study predominant genotype was 1 (33 cases, 83%), followed by genotype-3 (6 cases, 15%) and 4 (1 case, 3%). SVR12 rates as per genotype were 67%, 100% and 0% in genotype-1, 3 and 4. Another study¹⁴ with compassionate use of SOF had reported SVR12 rates of 74% among those who were treated <12 months after transplantation and 43% in patients who had been treated >12 months after transplanted. We did not find difference between the groups <12 months and >12 months to be statistically significant among our patients.

Our results differ from those reported earlier due to several possible reasons. Firstly, the distribution of genotypes is different. Genotype-3 predominated in our patients whereas they were a minority in Charlton's study group.⁶ Secondly, none of our patients had cirrhosis. Liver biopsy finding reported by Charlton (F0 = 1, F1–F2 = 14,

F3 = 9, and F4 = 16) indicated that nearly 40% of their patients had cirrhosis. Lastly, our patients reported for treatment relatively early after transplantation. Charlton's patients had reported for treatment after a median of 4.3 years (1–10.6) after transplantation and there were very few patients without liver fibrosis.⁶ In our study, median time after transplantation was 11 months (range 1–95 months). Liver biopsies are not routinely done by us as protocol and Fibroscan as measure of liver stiffness showed median stiffness of 7 (with range from 3 to 11) which is equivalent to fibrosis score <F2.

SVR12 response seen among genotype-1 by us appears significantly better (100% vs. 67%) than that reported in other two papers. In Charlton's study, there was no difference between SVR12 and SVR24, while one of our patients with genotype-1 and having achieved SVR12, was found to have relapsed when tested 7 months after completion of treatment. In yet another multicenter open label study 31 of 57 patients had completed treatment and SVR4 rates were found to be 90% and 60% in patients with genotype-2 and genotype-3 respectively.¹⁵

We have come a long way from the time when physicians only had regimens with drugs like Peg-IFN-Alfa, RBV, telaprevir, and boceprevir, which had been of limited efficacy and tolerability in studies of liver transplant recipients with recurrent HCV.^{16–18} Interferon plus RBV regimens were poorly tolerated and showed dismal results.⁵ In one study of 53 patients with recurrent HCV infection post LT treated with Peg-IFN a2b and RBV only 14 achieved SVR (26%).¹⁹ During 1-year period between 2015 and 2016, several new directly acting antiviral drugs have become available.^{20,21} A fixed drug combination of SOF and ledipasvir for treatment of genotype-1²² and a combination of SOF and daclatasvir for genotype-3²³ have now been marketed with affordable price-tag in India. These regimens have also been found to safe and effective for treatment of HCV in general and can avoid the hematological side effects seen with RBV. It remains to be seen if RBV free regimens will fare as well as RBV containing regimens in special situations. Need for use of RBV has been emphasized by many recent recommendations for the post liver transplant group.^{24–27} However, a combination of SOF and weight based RBV given over 24 weeks remains an effective, low cost alternate regimen devoid of any drug interactions.

Another approach to treating post transplant recurrence has been pre-emptive treatment. The concept of pre-emptive treatment was introduced because recurrent HCV infection follows an aggressive course with 10–30% of them developing cirrhosis within 5 years, and more than 40% developing cirrhosis within 10 years.^{1,28} Rates of graft loss and patient mortality are also markedly higher for patients with recurrent HCV than for uninfected patients, and re-transplantation frequently is associated with a poor outcome.²⁹ A meta-analysis of 10 randomized trials with

441 patients who underwent LT for chronic HCV infection found no differences in patient survival, graft rejection, re-transplantation, or HCV recurrence between patients who received antiviral therapy following transplantation and those who did not. But this included trials done during Peg-IFN era.³⁰ A randomized trial with 115 patients not included in the meta-analysis compared early post-transplantation prophylactic therapy with treatment only once there was histologic recurrence (histological activity index ≥ 3 and/or fibrosis score ≥ 2 on liver biopsy) found no clear benefit to the pre-emptive approach.³¹ Interferon free DAA regimen is devoid of significant side effects and can easily be used as presumptive therapy. Studies following that thought will be interesting.

In conclusion, we found an excellent response to treatment with 24 weeks of SOF and RBV among patients with non-cirrhotic recurrent hepatitis C (genotype-3 and 1) after LDLT in South Asia. Our SVR rates are much superior to those reported earlier mainly because patients were non cirrhotic and were treated relatively early after transplantation. Although, availability of newer DAAs is replacing this regimen in latest guidelines, it remains an effective regimen for the group of patients studied. These findings are important as they show that a low cost regimen with near zero risk of drug interactions remains effective in post transplant HCV recurrence provided patients report early for treatment before cirrhosis/fibrosis has developed and remains relevant for resource constrained settings.

CONFLICTS OF INTEREST

The authors have none to declare.

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