Efficacy and safety of an interferon-free regimen for treatment of recurrent hepatitis C virus infection following liver transplant

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Introduction
Recurrent hepatitis C virus (HCV) infection after transplantation is aggressive, and its progression to cirrhosis is more rapid than in nontransplant settings. As pegylated interferon based therapies for HCV treatment after transplantation have poor tolerance, poor efficacy, and significant interactions with immunosuppression medications, and this developed the need for a new safe and effective oral regimen.

Aim
To evaluate the efficacy, safety, and tolerability of sofosbuvir (SOF) in combination with ribavirin (RBV) in treating recurrent hepatitis C after transplantation and also to detect any significant interaction with immunosuppressive therapy.

Patients and methods
Between August 2014 and January 2016, a single-center, prospective, nonrandomized, open-labeled study was conducted, in which the patients with post-transplant recurrent HCV infection were enrolled. All patients received 400 mg once-daily SOF for 24 weeks with variable dose of RBV. After treatment, patients underwent follow-up for 12 weeks.

Results
Sixty patients were enrolled, and their mean age was 57.67 years, with 78.3% were male. Overall, 70% had genotype 1 and 61.7% had received previous HCV treatment. At baseline, 21 patients had severe fibrosis. Median time interval from liver transplantation was 51 months, and immunosuppressive therapy was tacrolimus based in 78.3%. Median baseline HCV-RNA was 2.341.172 IU/ml. Among the patients, 12-week sustained virological response was achieved in 43 (71.7%) patients. There was no significant difference in dose and level of tacrolimus during course of therapy. Absence of hepatic encephalopathy, treatment-naive patients, nonsevere fibrosis, and low pretherapy Liver stiffness (LS) values were predictors for sustained virological response.

Conclusion
Interferon-free regimen containing SOF and RBV is generally safe, well tolerated, and reasonably effective in post-transplantation settings.

Keywords:
direct-acting antiviral agents, hepatitis C virus, liver transplantation, recurrent, sofosbuvir

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Introduction

Hepatitis C virus (HCV) is the most frequent indication for liver transplantation (LT), comprising ~40–50% of all cases [1,2].

Recurrence of hepatitis C viremia following LT occurs in all patients with chronic HCV infection who have detectable serum HCV RNA levels before transplant [3]. Up to 30% of patients may subsequently develop chronic hepatitis, characterized by progressive fibrosis leading to cirrhosis within 5 years [4].

To achieve the goal of optimal patient and allograft survival in patients with HCV-related liver cirrhosis undergoing LT, several strategies have emerged, including donor selection, close histologic monitoring, steroid-sparing immunosuppression, and effective and safe antiviral agents during the transplant settings. Pegylated interferon (Peg-IFN)-based therapies for HCV treatment used after transplantation have poor tolerance, poor efficacy, severe adverse reactions, and significant interactions with immunosuppression medications, and this developed the need for a new safe and effective all-oral regimen.

Till the time of our study conduction, few studies addressed the efficacy and tolerability of direct-acting antiviral agents based regimens in treating recurrent HCV infection after transplantation especially in the early post-transplant period.

The aim of the current study is to evaluate the efficacy, safety, and tolerability of sofosbuvir (SOF) in combination with ribavirin (RBV) in treating established recurrent hepatitis C after LT and to determine the predictors of response to antiviral therapy and detect significant interaction with immunosuppressive drugs.

Patients and methods

Patients recruitment and study setting

The study was conducted in the Multivisceral Transplant Unit in Padova University Hospital, Italy, between August 2014 and January 2016. It included 60 patients with post-transplant recurrent HCV-related liver disease who were diagnosed by PCR during their follow-up.

Before recruitment, all patients were informed with aim of the study and the possible complications of the drugs used. A consent was taken from all patients, and the study protocol was approved by Assiut and Padova Medical School Ethical Review Board.

Inclusion criteria

The inclusion criteria were as follows:

(1) LT of at least 3 months before enrollment
(2) Treatment-naive or experienced
(3) Primary or secondary LT
(4) Living or cadaveric donor LT
(5) Liver alone or liver-kidney transplant
(6) Absence of organ rejection.

Exclusion criteria

The exclusion criteria were as follows:

(1) Creatinine clearance more than 2.5 × Upper limit of normal (ULN)
(2) White blood cells more than 20 × 10^9/l
(3) Hemoglobin level (Hb) less than 9 g/dl
(4) The presence of hepatocellular carcinoma (HCC)
(5) Patients with limited life expectancy owing to non-liver-related comorbidities, for example, advanced malignancy or cardiopulmonary disease.

Study design

This was a unicenter, single-arm, prospective, nonrandomized, open-labeled study. All patients were subjected to detailed medical history, complete clinical examination, abdominal ultrasonographic scan, and pretreatment routine laboratory investigations, including liver function panel, serum creatinine, international normalized ratio, Hb level, and platelets count (in addition to baseline HCV RNA and genotype of HCV). All patients received 400-mg once-daily SOF (Gilead Sciences, Foster City, California, USA) for 24 weeks with variable dose of RBV, from 200 to 1200 mg based on patient tolerability (determined by Hb levels) with a median dose of 800 mg. After treatment, patients underwent follow-up for 12 weeks.

Protocol of ribavirin use

An initial dose of 800 mg/day was used, but it was increased to 1000–1200 mg in patients with pretreatment Hb level more than 14 g/dl and reduced to 400–600 mg if Hb up to 10 g/dl, with concurrent administration of subcutaneous erythropoietin (EPO).

Hb level was evaluated at week 1 and every month during antiviral therapy. RBV dose reduction would be implemented if Hb level was decreasing, keeping Hb level more than 10 g/dl. EPO was also given at a dose of 10 000 IU/week if Hb level decreased less than 10 g/dl even after reducing RBV dose.

RBV was suspended in case of persistent anemia (Hb<8.5 g/dl), in spite of RBV dose reduction and EPO administration.

Immunosuppression protocol

Calcineurin inhibitors (especially tacrolimus) were the backbone of immunosuppressive therapy in the current study. For patients with Child–Pugh B or C, corticosteroid had been started intraoperatively and gradually withdrawn within 6 months. Basiliximab (Novartis Pharmaceuticals Corp, Basel, Switzerland; Abbott, Illinois, USA) was given intraoperatively and at day 4. Tacrolimus was initiated at day 5, continued indefinitely, and the dose was adjusted according to the target trough level. Mycophenolate mofetil was used as part of the initial triple immunosuppressive therapy. Regarding Child–Pugh A patients, dual therapy consisting of corticosteroid and tacrolimus was used. Tacrolimus was initiated at day 1, with higher target trough level.

Efficacy and safety assessment

Quantitative PCR for HCV RNA was performed every 4 weeks, at end of the treatment, after 4 weeks, and lastly 12 weeks after termination of treatment. A sensitive quantitative assessment of the viral load was applied (Abbott RealTime, this assay had a lower threshold of detection of 12 IU/ml). Monthly follow-up during treatment included regular documentation for data on graft survival, graft function, incidence of acute cellular rejection, and medication-related adverse events.

Follow-up of the patients continued up to 12 weeks after treatment, and post-therapy routine laboratory

investigations with abdominal ultrasonographic examination were done for all patients to evaluate the effect of viral eradication on reversibility of hepatic dysfunction and degree of clinical and biochemical improvement.

Stoppage rules in the study

Treatment was discontinued for patients with the following criteria:

(1) Confirmed HCV RNA plasma concentrations at or above the lower limit of quantification after two consecutive HCV RNA plasma concentrations below the lower limit of quantification
(2) Confirmed HCV RNA plasma concentrations more than 1 log increase from nadir
(3) In addition, treatment was stopped for patients with any of the following safety reasons: alanine transaminase (ALT) or aspartate transaminase (AST) more than 5 × baseline, ALT or AST more than 15 × ULN, total bilirubin more than 10 × ULN, total bilirubin more than 3 × baseline, any grade 2 or higher rash associated with constitutional symptoms, any nonlaboratory grade 4 event assessed as related to study treatment, progressing hepatic decompensation, or steroid-resistant acute cellular rejection (ACR).

Results

Demographic and baseline characteristics of the studied patients

Table 1 showed demographic characteristics of the studied patients. The mean ± SD age was 57.67 ± 8.57 years, and most patients (78.3%) were males. Thirty-two (53.3%) patients were overweight, with mean ± SD BMI for all patients was 25.62 ± 3.14 kg/m^2.

The median duration from transplantation till time of this study was 51 months. Three (5%) patients had a history of liver retransplantation; the first patient was retransplanted for primary graft nonfunction, the second one had HCV related End stage liver disease (ESLD) after a primary transplantation, whereas the third patient was retransplanted for secondary biliary cirrhosis. Only one patient underwent combined liver and kidney transplantation owing to the presence of HCC on top of HCV-related liver cirrhosis and chronic kidney disease.

Previous post-transplantation antiviral therapy was recorded in 37/60 (61.7%); 33/60 (55%) received both RBV and Peg-IFN, and only 4/60 (6.7%) received RBV only.

Table 1 Demographic and baseline characteristics of the studied patients

Variables	*n*=60
Age (years)	57.67±8.57
>60	24 (40)
≤60	36 (60)
Sex	
Male	47 (78.3)
Female	13 (21.7)
BMI (kg/m^2)	25.62±3.14
Normal	28 (46.6)
Overweight	32 (53.3)
Duration of LT (months)	51 (5-284)
Liver retransplantation	3 (5)
Previous post-transplantation therapy	37 (61.7)
RBV alone	4 (6.7)
Peg-IFN + RBV	33 (55)
Outcome of the previous antiviral therapy (Peg-IFN + RBV)	
No response	23/33 (69.7)
Relapse	7/33 (21.2)
Intolerance	3/33 (9.1)
HE	
No	57 (95)
Grade I	1 (1.7)
Grade II	2 (3.3)
Jaundice	5 (8.3)
Ascites	
No	52 (86.6)
Minimal	1 (1.7)
Mild	6 (10)
Moderate	1 (1.7)
Tac-based immunosuppression	47 (78.3)
Genotypes	
1a	14 (23.3)
1b	28 (46.6)
2	4 (6.7)
3	10 (16.7)
4	4 (6.7)

Categorical data were expressed in the form of frequency (percentage) whereas continuous data were in the form of mean±SD or median (range) as appropriate according to normality test. HE, hepatic encephalopathy; LT, liver transplant/transplantation; Peg-IFN, pegylated interferon; RBV, ribavirin; Tac, tacrolimus.

Only three (5%) patients had hepatic encephalopathy (HE) before starting the therapy; two of them had grade II HE and the other patient had grade I. Jaundice was observed in 5/60 (8.3%) patients before starting therapy.

Fifty-two (86.6%) patients had no ascites at the baseline ultrasonographic examination, whereas minimal, mild, and moderate ascites presented in one (1.7), six (10%), and one (1.7%) patients, respectively. Regarding immunosuppressive therapy, it was tacrolimus based in 47/60 (78.3%) patients. It was noticed that most patients (28/60; 46.6%) had HCV genotype 1b, whereas other genotypes 1a, 3, 2, and 4 presented in 14 (23.3%), 10 (16.7%), four (6.7%), and four (6.7%) patients, respectively.

Response to antiviral therapy

The current study showed that 43/60 (71.7%) patients had 12-week sustained virological response (SVR) whereas the other 17/60 (28.3%) failed to achieve (Fig. 1). The response to 24-week dual therapy of SOF and RBV in different months of treatment and follow-up are shown in Fig. 2.

Effect of therapy on liver enzymes and function

Regarding ALT, AST, and alkaline phosphatase, there was a significant decrease in the level of these enzymes at week 12 after therapy, where *P* value was 0.00, 0.03 and 0.00, respectively, whereas bilirubin, international normalized ratio, and γ-glutamyl transpeptidase (GGT) had no significant differences. Albumin level was significantly increased [38.65 (23–41) vs. 40.86 (31–43) g/dl; $P = 0.00$], and only one (1.7%) patient had persistent ascites 12 weeks after therapy ($P = 0.00$), with subsequent significant improvement of Child–Pugh score ($P = 0.00$) (Table 2).

Adverse effects

Most studied patients had no major adverse effects that led to stoppage of the therapy or death. Of 60 patients, 35 (58.3%) patients experienced adverse effects during the time of the study. Ten (16.7%) patients experienced asthenia, whereas fatigue occurred in four (6.7%) patients. Dyspnea was reported in five (8.3%) patients. Rash, nausea, tremors, itching, and insomnia, all of them were reported in two (3.3%) patients for each (Table 3).

Other less frequent adverse effects that were reported in one (1.7%) patients for each were herpes zoster, headache, hand erythema, constipation, diarrhea, and loss hair.

Anemia was the most frequent adverse effects where it occurred in 23/60 (38.3%) patients during the time of the study. These patients needed modification of RBV dose with or without EPO injection. and only one (1.7%) patient received blood transfusion, yet three (5%) patients had to stop RBV because of persistent anemia.

All adverse effects improved after end of therapy without any specific treatment or intervention except for herpes zoster infection (treated by acyclovir) and anemia (which was managed as mentioned previously).

Predictors of sustained virological response

On univariate analysis, it was found that absence of HE, treatment-naive patients, nonsevere fibrosis, low pretherapy LS values, and high baseline GGT level were associated with increased SVR. On the contrary, based on multivariate regression analysis, the independent risk factors for failure to achieve SVR were previous therapy, HE at baseline, severe fibrosis (>F3), and high pretreatment LS measurements, whereas baseline GGT had no effect on SVR (Table 4).

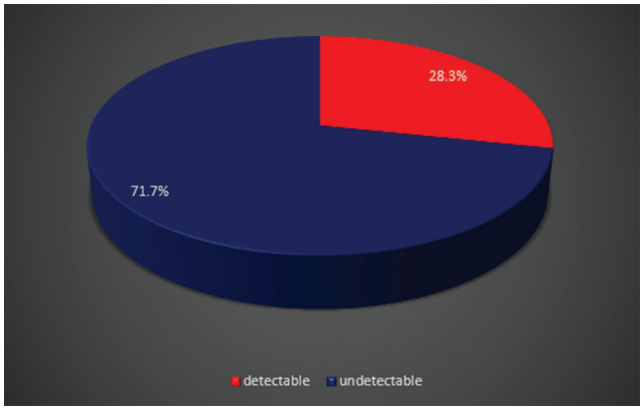
The effect of antiviral therapy on the level and the dose of tacrolimus

Regarding the effect of used regimen on the level and the dose of tacrolimus during the course of antiviral therapy, the current study showed that there was no significant difference in dose and level of tacrolimus during course of therapy, with $P = 0.95$ and 0.17 for dose and level of tacrolimus, respectively (Table 5).

Discussion

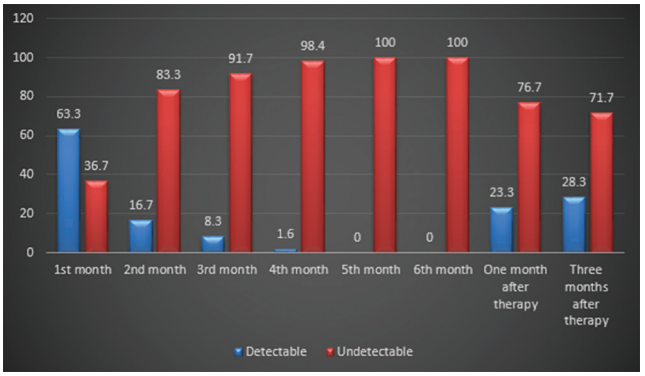
The major indication for LT in North America and Western Europe is liver disease resulting from chronic infection with HCV [5]. In Egypt, HCV infection is a major health concern [6]. The prevalence of HCV among the 15 – 59-year age group is estimated to be 10% (the highest prevalence in the world) [7].

Figure 1



12-week post-treatment hepatitis C virus RNA.

Figure 2



The response during and after treatment.

Table 2 Comparison between baseline and 12-week post-therapy data

Variables	Before therapy	3 Months after therapy	*P*
Bilirubin (μmol/l)	14.55 (5.10-313)	14.30 (5.10-54)	0.33
ALT (U/l)	85 (22-467)	34.5 (9-180)	0.00
AST (U/l)	74.50 (17-738)	20 (23-177)	0.03
GGT (U/l)	73.5 (17-885)	61 (7-874)	0.55
ALP (U/l)	115 (64-643)	90 (38-638)	0.00
Albumin (g/l)	38.65 (23-41)	40.86 (31-43)	0.00
INR	1.08 (0.9-2.2)	1.07 (0.94-1.3)	0.45
Ascites	8 (13.4)	1 (1.7)	0.00
Child score	5 (5-9)	5 (5-7)	0.00
MELD score	8 (6-22)	8.6 (6-16)	0.53

Data were expressed in the form of median (range). ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ-glutamyl transpeptidase; Hb, hemoglobin; INR, international normalized ratio; MELD, model for end-stage liver disease.

Table 3 Treatment-related adverse effects and hematological abnormalities

Adverse events	*n* (%)
Patients with any adverse events	35 (58.3)
Patients with serious adverse events	0
Patients stopped treatment	0
Deaths	0
Anemia	23 (38.3)
Asthenia	10 (16.7)
Dyspnea	5 (8.3)
Fatigue	4 (6.7)
Cutaneous rash	2 (3.3)
Anorexia and nausea	2 (3.3)
Tremors	2 (3.3)
Itching	2 (3.3)
Insomnia	2 (3.3)
Herpes zoster	1 (1.7)
Headache	1 (1.7)
Hand erythema	1 (1.7)
Loss of hair	1 (1.7)
Diarrhea	1 (1.7)
Constipation	1 (1.7)
Thrombocytopenia	1 (1.7)

Data were expressed in the form of frequency (percentage).

Table 4 Multivariate regression analysis for the predictors of sustained virological response

Predictors	OR	95% CI	*P*
Previous therapy	**2.33**	**1.1-1.5**	**0.02**
Severe fibrosis (>F3)	4.47	1.8-5.34	**0.01**
Presence of HE	2.33	2.56-3.01	**0.00**
GGT	0.9	0.9-1.1	0.27
FibroScan (kPa)	1.2	1.1-2.8	**0.00**

P<0.05, significant. CI, confidence interval; GGT, γ-glutamyl transpeptidase; HE, hepatic encephalopathy; OR, odd ratio. Fibroscan, Echosens, Paris, France.

Table 5 Effect of therapy on level and dose of tacrolimus during course of therapy

Variables	Dose	Level
Before therapy	1 (0.5-5)	4.2 (0-8.7)
During first month	1 (0.5-5)	4.2 (1.2-8.3)
During second month	1 (0.5-5)	4 (0-8.6)
During third month	1 (0.5-5)	4.3 (0-10)
During fourth month	1 (0.5-5)	4.29 (0-9.4)
During fifth month	1 (0.5-5)	4.65 (2.4-7.9)
During sixth month	1 (0.5-5)	4.25 (2.03-7)
P	0.95	0.17

Data were expressed in the form of median (range). *P*<0.05, significant.

The high prevalence of HCV-related chronic liver diseases has led to increasing numbers of Egyptian patients experiencing ESLD, necessitating LT; most indications (64%) were HCV related [6].

For patients with detectable serum levels of HCV RNA at the time of transplantation, recurrence of HCV infection is immediate and universal [8]. Recurrent HCV infection after transplantation is generally aggressive, and progression to cirrhosis and decompensation is more rapid than in patients with HCV who have not been transplanted [9].

Treatment options for patients with recurrent HCV after transplantation were limited. For patients with severe recurrence, IFN-based regimens are difficult to tolerate and have disappointing efficacy with hard-to-manage drug interactions [10]. Triple-therapy regimens with protease inhibitors have been shown to improve efficacy but exacerbate the adverse effects of treatment and are complicated to be administered with immunosuppressive drugs [11].

Therefore, there is a great need for a more-potent as well as more-tolerable regimen without drug interactions for LT recipients with recurrent HCV. SOF is a potent inhibitor of the HCV NS5B polymerase. SOF has been approved in combination with RBV, with or without Peg-IFN, for the treatment of CHC genotypes 1–6 [12]. SOF has pan-genotypic activity, a high genetic barrier to resistance, and a favorable safety profile. Most adverse reactions reported in clinical studies with SOF have been attributable to the concurrent use of Peg-IFN or RBV [13].

SOF plus RBV for up to 48 weeks was indicated for patients with HCV and HCC awaiting LT. Curry *et al.* [14], in a phase 2, open-label study, enrolled patients with HCV of any genotype and cirrhosis who were on waitlists for transplantation for HCC, and they received up to 48 weeks of SOF (400 mg) and RBV before LT. Of 43 patients who had undetectable HCV at the time of LT, 30 (70%) had a post-transplantation virologic response at 12 weeks. Recurrence was related inversely to the number of consecutive days of undetectable HCV RNA before transplantation.

Real-life data regarding the safety profile, tolerability, and effectiveness of SOF-based regimens in the

organ transplant recipients are limited, especially in early post-transplantation period. Our single-arm prospective cohort emerged to evaluate the efficacy and the tolerability of a combination of 400-mg SOF and median dose of 800 mg RBV for 24 weeks for post-transplant patients with documented recurrent hepatitis C who were followed for another 12 weeks after treatment.

From August 2014 till January 2016, 60 patients were enrolled, 78.3% were male, 70% had genotype 1, and 61.7% received previous HCV treatment. At baseline, 21 (35%) patients had severe fibrosis according to Ishak score. The median time interval from LT was 51 months (5–284), and immunosuppressive therapy was tacrolimus based in 78.3%. The median baseline HCV-RNA was 2.341.172 IU/ml (770–52 330 800 IU/ml). SVR at 12 weeks after therapy was achieved in 43 of 60 patients (71.7%). The response rate in our study is consistent with the rate that was reported by Charlton *et al.* (2015) and Faisal and colleagues [15].

Compatible results were reported in a study that was conducted in Ain Sham University Hospital, Egypt. Thirty-nine Egyptian Living donor liver transplant (LDLT) recipients were treated for recurrent HCV after LDLT with SOF and RBV without Peg-IFN for 6 months. SVR at week 12 after End of therapy (EOT) was achieved in 76% (29/38) of recipients [16].

In contrast, a study was conducted by Forns *et al.* [17] that demonstrated lower SVR at 12 weeks after treatment. In that study, 104 patients received 24–48 weeks of SOF and RBV, and investigators added Peg-INF to the regimen at their discretion. Overall, the SVR12, excluding patients who underwent retransplantation (n = 12), was 56% (54 of 92) for patients who received SOF-RBV. Such low response rate was attributed to two factors; the retransplanted patients who were not involved in the final evaluation of the efficacy and high prevalence of advanced fibrosis in the study population (50% had cirrhosis). Therefore, SVR12 was further evaluated in cirrhotic versus noncirrhotic cases, and it was 43% (16 of 37) versus 74% (25 of 34), respectively.

On the contrary, higher efficacy of SOF and RBV in treating HCV recurrence after LT was documented in another Egyptian study in which Yosry *et al.* [18] enrolled 157 patients with HCV recurrence after LDLT from November 2014 to December 2015. SVR12 in SOF+RBV regimen was 84.9%. The increase in SVR12 may be related to ethnic factors and less number of treatment-experienced patients in comparison with previous studies, and also the variation in the predominant HCV genotype; genotype 1 was the major one in all previous non-Egyptian studies, including ours, whereas genotype 4 has the highest prevalence in Egypt and middle east [19,20].

On univariate analysis in the current study, HE, the baseline level of GGT, previous therapy, pretreatment LS values, and degree of histological fibrosis had significant effect on SVR ($P < 0.05$).

Multivariate regression analysis was done for the studied population to detect the factors that independently predict SVR, and it revealed that the major factors that associated with increased response rates were absence of HE, treatment-naive patients, absence of advanced fibrosis, and low pretreatment LS.

Regarding the effect of both hepatic fibrosis and previous post-transplant therapy on SVR, similar results were reported by Dabbous *et al.* [16] and Yosry *et al.* [18]; however, Faisal *et al.* [21] found that the patients who previously failed PEG-IFN and RBV with or without first-generation protease inhibitors regimens after transplantation had lower SVR12 rates compared with the treatment experienced only before transplant (74 vs. 92%; P = 0.04; 95% confidence interval: 0.61–0.87) and showed that the patients with severe fibrosis had numerically lower SVR12 rates than those with F0–F2, but without significant difference (81 vs. 92%; P = NS).

With respect to the safety profile in this cohort, the combination of SOF and RBV appeared to be well tolerated in most patients, where no deaths, graft losses, episodes of acute rejection, or serious adverse effects, leading to stoppage of the therapy (SOF) had been reported. The incidence and degree of the adverse effects are comparable to that reported in the published international trials using the same regimen and with the same doses.

We found no significant difference in the dose and the level of the tacrolimus during the course of the therapy, with P = 0.95 and 0.17 for the dose and the level, respectively. The same was reported by the study by Faisal *et al.* [21], as calcineurin inhibitors are substrates of cytochrome P450 3A and P-glycoprotein, neither of which are inhibited or induced by SOF. The lack of effect of SOF on the metabolism of immunosuppressive agents is an important factor for the tolerability, safety and, hence, efficacy of SOF in the post-transplantation settings.

The current work had some limitations. The small sample size was one of the drawbacks of the present cohort, as only 60 patients were involved in the study, and therefore, such sample size did not allow the

optimal subgroup comparison. The patients who had genotype 1 were 42/60 (70%), whereas those who had genotype 4 were only four (6.7%) patients. The uneven presentation of different HCV genotypes in the study population might prevent us to detect the actual effect of viral genotype on SVR. Our cohort is a single-arm study as there was no control or comparison group. There was a lack of data concerning the previous HCV treatment before transplantation, which may have a direct effect on the response rate to the current SOF-based regimen. The emergence of multiple direct-acting antiviral agents and their approval in treating HCV infection in nontransplant and post-transplant settings will restrict the use of RBV but does not abolish its role or lessen the importance of our study, as SOF is still the backbone in most of HCV treatment regimens.

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Conflicts of interest
There are no conflicts of interest.

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