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RESEARCH ARTICLE

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Efficacy and safety of sofosbuvir-based therapy in hepatitis C virus recurrence post living donor liver transplant: A real life egyptian experience

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Background and Aim: Direct acting antiviral has offered treatment of hepatitis C virus (HCV) recurrence post liver transplantation (LT) with an all-oral regimen for short duration, excellent safety profile, and high sustained virological response (SVR). The aim of this study was to evaluate the efficacy and safety of sofosbuvir (SOF)-based regimens in the real world among a cohort of Egyptian patients with recurrent HCV post living donor LT (LDLT).

Methods: Patients with HCV-G4 recurrence post-LDLT were recruited from National Committee of Control of Viral Hepatitis, Egypt, from November 2014 to May 2017. They received different SOF-based regimens according to the treatment protocols available during this period. Patients' outcome and Adverse effects (AE) were evaluated.

Results: One hundred ninety patients (170 males, mean age 56.8 ± 7.9 years) were included. Calcineurin inhibitors were the main immunosuppression used (173 patients). Out of 190, 119 (62.6%) received SOF/ribavirin (RBV), 38 (20%) SOF/simeprevir (SMV), 22 (11.6%) SOF/daclatasvir (DSV)/ ± RBV, and 11 (5.8%) received SOF/LDV/ ± RBV. Overall SVR12 was 89.5%, 84.9% in SOF/RBV group, 94.7% in SOF/SMV, 100% in SOF/DCV, and 100% in SOF/LDV with no statistically significant difference ($P = 0.104$). The AE reported were as follows: anemia (n = 65, 34.4%) mainly in SOF/RBV group, transient hyperbilirubinemia during SOF/SMV in 13 patients (34%), mild Acute cellular rejection in eight patients (4.2%), and hepatocellular carcinoma in two patients (1%) mainly driven by underlying liver condition. Two deaths were unlikely related to HCV therapy.

Conclusion: Different SOF-based regimens were effective with high SVR12 rates in a difficult-to-treat population, recurrent HCV post LDLT.

KEYWORDS
DAAs, efficacy and safety, HCV, LDLT

Abbreviations: ACR, acute cellular rejection; DAAsd, rect acting antiviral; DCV, daclatasvir; HCC, hepatocellular carcinoma; LDLT, living donor LT; LDV, ledipasvir; LT, liver transplantation; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response.

1 | BACKGROUND

In Egypt, HCV viraemic prevalence was estimated to be 7.3% according to a mathematical model that was used to estimate the 2013 HCV infected populations.[1] HCV is considered to be the main cause of end-stage liver disease and the most common indication for liver transplantation (LT). However, HCV recurrence post-transplant is almost universal and is the common cause of liver graft loss and death in liver transplant patients infected with HCV.

Rapid advances in direct-acting antivirals (DAAs) in the last few years have completely changed the paradigm of hepatitis C therapy. Recent studies have shown that LT recipients can be safely and effectively treated with DAA combination therapies.[2,3] The appearance of new DAAs has offered treatment of HCV recurrence post LT with an all-oral regimen for short duration of therapy with few adverse effects and high cure rates.

The aim of this study was to evaluate the efficacy sustained virological response 12 weeks posttreatment (SVR12) and safety of different sofosbuvir (SOF)-based DAAs regimens in a real-world setting among a cohort of Egyptian patients with recurrent HCV infection after living donor liver transplantation (LDLT).

2 | PATIENTS AND METHODS

2.1 | Study design and study population

This study is a retrospective analysis of a prospective cohort of adult patients with recurrent HCV post LDLT (n = 190) who were recruited from the National Hepatology & Tropical Medicine Research Institute, Cairo, Egypt, one of the largest centers for treatment of viral hepatitis affiliated to the Minstry of Health And Population (MOHP). Patients were referred from several centers of LDLT in Egypt from November 2014 to May 2017. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study had been approved by the institutional ethical committee and data were obtained from patients' medical records.

3 | PATIENT COHORT AND DATA COLLECTION

3.1 | Inclusion criteria

Patients were included according to the inclusion criteria approved by the National Committee for Control of Viral Hepatitis (NCCVH): age 18 to 65 years (both genders), positive HCV-RNA at the time of inclusion, both treatment naive and treatment experienced (pre LT IFN-based or post LT DAAs therapy), compensated recurrent HCV + /-cirrhosis with no evidence of rejection, vascular or biliary complications at the time of starting DDAs, and at least 6 months duration after LT. All patients included had HCV genotype 4.

3.2 | Exclusion criteria

Non-HCV related causes for LT, pregnancy or breastfeeding, substance abuse, IV drugs or drug-related liver disease, and patients who are ineligible for available hepatitis C treatments.

3.3 | Methodology

Data about the liver transplant was retrieved from medical records of HCV patients who received all oral, IFN-free, and SOF-based therapy according to the treatment protocols accepted by the NCCVH at that time from November 2014 to May 2017. Because of the rapidly changing treatment options for HCV, treatment regimens were defined without reference to power/sample size calculation to provide a timely description of efficacy and safety of the available DAAs in LT recipients in real-life clinical practice. Standard doses of SOF, simeprevir (SMV), daclatasvir (DCV), SOF/ledipasvir (LDV), and ribavirin (RBV) were utilized. The decision to initiate treatment, selection of the treatment regimen (+ /− RBV), the dose of RBV, and the duration of therapy were solely the responsibilities of the treating clinician. All participants were followed up every 4 weeks during the treatment and thereafter for 12 weeks after the end of treatment (EOT) for laboratory analyses, monitoring of immunosuppressant level, and evaluation of side effects. The primary endpoint was SVR at week 12 (SVR12).

4 | DATA COLLECTION

Demographic, clinical, laboratory data, biopsy results if available, prior HCV treatment, co-morbid conditions, the presence of hepatocellular carcinoma (HCC) pre-LT, immunosuppressive therapies, transplant complications, and rejection episodes were collected throughout the treatment period and the posttreatment follow-up period until the determination of SVR12. Data concerning adverse events during DAA therapy was also obtained.

Data retrieved from patients' medical records included:

1. Descriptive data:

- Age, gender and body mass index (BMI).
- Pre LT medical problems, hypertension, diabetes mellitus, and presence of HCC with or without portal vein thrombosis (PVT).
- The duration between LT and the start of treatment.
- Complications post LT and before starting DAA treatment; biliary, vascular complications or rejection.
- Current immunosuppression regimen.

2. Baseline laboratory investigations: complete blood count; liver biochemical profile: total and direct bilirubin AST, ALT, ALP, GGT, albumin, INR, serum creatinine, HbA1c, serum AFP, and HCV RNA by polymerase chain reaction (PCR) and immunosuppressant level.
3. Transient Elastography (TE, FibroScan Echosens, Paris, France) results and liver biopsy whenever available. The cut-off of

liver-stiffness used to significant fibrosis (≥F2) was defined as 8.5 Kpa (according to Carrion et al and Kamphues et al).[4-6] The METAVIR scoring system was used to assess stages of fibrosis (F).

4. Follow up at EOT and 12 weeks post-treatment (SVR12) including:
   - •Data of adverse events.
   - •Follow up labs including CBC, liver biochemical profile, creatinine, immunosuppression level, and HCV-RNA by PCR.

4.1 | Treatment efficacy

Treatment efficacy depended upon the achievement of SVR12 (HCV-RNA level below the level of quantitation, serum HCV-RNA was measured using the Cobas Ampli Prep/Cobas TaqMan HCV-RNA assay [Roche Diagnostics, Pleasanton, CA] with a lower limit of detection of 15 IU/ml; recorded 12 weeks after treatment discontinuation) on an intention to treat (ITT) analysis. Patients who were lost to post-treatment follow up or who discontinued therapy early due to a virological failure were counted as treatment failures.

4.2 | Safety

adverse events (AEs) were defined as any event that required medication dose reduction or discontinuation, or the addition of a concomitant medication for management.

5 | TREATMENT REGIMENS

All patients with recurrent HCV post-LDLT received and completed a 12 or 24-weeks different SOF-based DAA therapy.

1. SFV 400 mg daily plus RBV for 24 weeks (n = 119). Initial RBV dose was 200 mg/day with a weekly increase by 200 mg according to hemoglobin (Hb) levels to reach 800 mg/day at week 4, if tolerated. An optimal dose of RBV; 1000 mg (if < 75 kg) or 1200 mg (if ≥ 75 kg). Only one patient tolerated 1200 mg of RBV. Dose reduction of RBV was a 200 mg stepwise decrease if Hb was less than 10 g/dL; RBV was discontinued with the addition of erythropoietin if Hb was less than 8.5 g/dL and blood transfusion at ≤ Hb 7 gm/dl.
2. SFV 400 mg once daily plus SMV 150 mg once daily orally for 12 weeks (n = 38) without RBV.
3. SFV 400 mg once daily plus DCV 60 mg once daily orally ± RBV for 12 to 24 weeks (n = 22). Nine patients in SOF/DCV group received 12-week regimen (three of them, being cirrhotics, received RBV), while 13 received 24-week regimen with RBV (being prior SOF-based relapsers). RBV initial dose was 600 mg.
4. Fixed-dose combination of SOF/LDV 400/90 mg once daily orally without RBV for 24 weeks (n = 11). Only two patients (n = 2/11) received RBV with SOF/LDV for 24 weeks (being prior SOF-based relapsers). RBV initial dose was 600 mg.

5.1 | Statistical analysis

Patients were stratified according to treatment response into responders (RS) and non-responders (NR). Continuous variables were presented by mean and SD for parametric data and by median and interquartile range (IQR) for nonparametric data. Baseline data were compared based on treatment protocols by unpaired t-student test or the Mann-Whitney U test for continuous data and by chi-square or Fischer's exact test for categorical data. In all tests, the *P* value was considered significant if less than 0.05.

6 | RESULTS

A total of 190 patients with recurrent HCV post LDLT; mean age 56.8 ± 7.9 years; 170 males (89.5%). Overall baseline characteristics of the whole studied group were shown in Table 1.

Out of 190 patients, 119 (62.6%) received SOF/RBV, 38 (20%) received SOF/SMV, 22 (11.6%) received SOF/DCV/±RBV (including 13 who were prior SOF/RBV treatment failures), while 11 (5.8%) received SOF/LDV/±RBV (including two who were prior SOF/RBV relapsers).

7 | TREATMENT OUTCOME AND EFFICACY

Overall SVR12 on ITT analysis was achieved in 170/190 patients (89.5%), being 101/119 patients (84.9%) in SOF/RBV group; 36/38 patients (94.7%) in SOF/SMV group; 22/22 patients (100%) in SOF/DCV and 11/11 (100%) in SOF/LDV. However, there was no statistically significant difference in SVR12 between the four groups (*P* value = 0.104; Table 2 and Figure 1).

Overall achievement of SVR12 was statistically related to the interval between LT and the start of antiviral therapy and the history of prior IFN-based therapy pre LT. The shorter duration between LT and start of antiviral therapy (4.5 ± 3.48 vs 6.79 ± 3.78 years) and negative history of prior IFN-based therapy pre LT were significantly associated with SVR12 (*P* value; 0.02 and 0.004, respectively). Meanwhile, SVR12 was not statistically related to demographic data, co-morbidities, pre-LT HCC, vascular, biliary complications, and rejection occurring pre DAA therapy. In addition, prior SOF-based therapy failure post LT was not associated with a significant difference between RS and NR (Table 3).

Baseline laboratory data and viral load showed no statistically significant difference between RS and NR groups apart from serum AFP. Patients who achieved SVR12 had a significant lower baseline serum AFP than non-responders (5.40 ± 6.30 ng/mL vs 16.31 ± 14.80 ng/mL respectively, *P* value 0.013) (Table 3).

There was no statistically significant difference between RS and NR regarding the stage of fibrosis (assessed by fibroscan) (*P* = 0.22).

TABLE 1 Overall demographic data and baseline characteristics of the whole study cohort with recurrent HCV post LT (n = 190)

Demographic data	
Age, y (mean ± SD)	56.8 ± 7.9
BMI, kg/m^2 (mean ± SD)	28.53 ± 6.57
Male, n (%)	170 (89.5%)
Pre-LT co-morbid conditions	N, %
Hypertension	73 (38.4%)
DM	101 (53.2%)
HCC before LT	38 (20%)
PVT	3 (1.6%)
Failure of IFN based therapy before LT, n (%)	60 (31.6%)
Failure of DAAs based therapy after LT, n (%)	15 (7.9%)
The interval between LT and start of DAA (mean ± SD), y	4.69 ± 3.54
Baseline labs, units	Mean ± SD
Hb, gm/dl	14.41 ± 2.5
TLC, 10^3/cmm	5.1 ± 2.1
PLT, 10^3/cmm	166 ± 71.8
Total bilirubin, mg/dl	1.01 ± 0.66
Direct bilirubin	0.14 ± 0.44
AST (U/L)	68.98 ± 56.46
Median and IQR	58 (62)
ALT, U/L	83.33 ± 82.35
Median and IQR	58 (94)
ALP, U/L	174.63 ± 151.87
Median and IQR	135 (117)
GGT, U/L	250 ± 348.7
Median and IQR	27 (190)
Serum albumin, gm/dl	4.01 ± 0.48
Prothrombin Concentration, %	92.6 ± 14.10
Creatinine, mg/dl	1.05 ± 0.28
HbA1c, %	6.60 ± 1.27
Serum AFP, ng/ml	6.51 ± 7.50
Median and IQR	4.2 (4.8)
HCV-RNA post LT(x10^6), IU/ml	4.75 ± 8.29
Median and IQR	1.47 (4.7)
HCV RNA log 10 post LT	6.07 ± 0.87
Complications post LT and before starting DAA treatment:	N, %
Vascular complications (PVT or HAT)	0 (0%)
Acute rejection	18 (9.5%)
Biliary complications (leak, stenosis)	40 (21.1%)
The severity of hepatic fibrosis	
Fibroscan Kilopascal, kPa (n = 139) mean ± SD	10.70 ± 9.17
Fibroscan	
≤F2	91 (65.5%)
>F2	48 (34.5%)
Biopsy (n = 25)	
≤F2 (n = 20)	20 (80%)

(Continues)

TABLE 1 (Continued)

Demographic data	
>F2 (n = 4)	4 (20%)
Immunosuppression drugs	N, %
Tacrolimus	131 (68.9%)
Cyclosporine	42 (22%)
Mycophenolate mofetil	41 (21.6%)
Sirolimus/evrolimus	36 (18.9%)

Available data for 139 patients only.
HAT, thromboses of the hepatic artery; IQR, interquartile range.

TABLE 2 Treatment outcome (SVR 12) in the study cohort with recurrent HCV patients post LT (n = 190) after SOF-based therapy

Treatment outcome	SOF/RBV 24 w, n = 119	SOF/SMV 12 w, n = 38	SOF/DCV ± RBV 12-24 w, n = 22	SOF/LDV ± RBV12-24 w, n = 11
EOT	111 (93.3%)	36 (94.7%)	22 (100%)	11 (100%)
SVR12	101 (84.9%)	36 (94.7%)	22 (100%)	11 (100%)
Treatment failures	18 (15.1%)	2 (5.3%)	0 (0%)	0 (0%)
• Primary failure	0	1	0	0
• Breakthrough	7	1	0	0
• Treatment discontinuation	1	0	0	0
• Relapser	10	0	0	0

8 | IMMUNOSUPPRESSION

Baseline tacrolimus level, which was the most common immunosuppression used (n = 131), showed no statistically significant difference between RS and NR groups ($P = 0.164$).

During the treatment, there was no deterioration in hepatic or renal function, no graft loss, no serious adverse events, no sign of graft rejection, and no toxic levels of immunosuppression. All potential drug-drug interactions of comedications were judged and modified before antiviral therapy. None of the patients who were on cyclosporine received SMV.

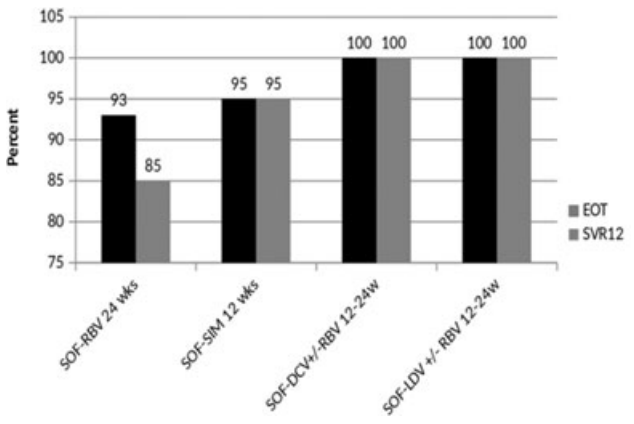

FIGURE 1 Treatment responses in patients with recurrent HCV after different SOF-based regimen. (P value = 0.104)

9 | SAFETY

All DAA regimens were generally well tolerated. Most reported adverse events (AEs) were mild to moderate in severity. Two deaths occurred; were unlikely related to HCV therapy.

One patient in the SOF/RBV group with uncontrolled diabetes mellitus (DM) and hypertension, chronic heavy cigarette smoker, had the cerebral stroke during week 8 of treatment. The initial blood pressure (BP) during hospital admission was 230/110, computed tomography (CT) brain scan revealed the middle cerebral artery (MCA) infarction. He had disturbed conscious level with GCS 7. After being ventilated, he developed bilateral bronchopneumonia with sepsis followed by death. This was not related to drugs used but was secondary to his medical comorbidities.

HCC: One patient in SOF/SMV group, was transplanted 2015 because of HCC outside Milan criteria. Four months post LT, he received a 12-week regimen of SOF/SMV and achieved EOT response. During his follow-up visit at week 8 post-treatment, his liver scan showed a hepatic focal lesion, which was further confirmed by Triphasic CT abdomen to be HCC. It was ablated by transcatheter arterial chemoembolization. However, his AFP kept rising to >1000 ng/dl. Further imaging revealed lymph nodes and bone metastases followed by patient death.

Another patient, in SOF/DCV group, had de-novo HCC. It was diagnosed in a cirrhotic patient who was transplanted in 2004. He was prior SOF/RBV relapser post LT. HCC developed after achieving SVR12 following SOF/DCV/RBV regimen for 6 months for which he had a resection.

TABLE 3 Comparison between RS and NR in SOF/RBV group regarding all baseline characteristics

Demographic data	RS (n = 101)	NR (n = 18)	*P*-value
Age, y (mean ± SD)	56.02 ± 7.73	56.33 ± 9.80	0.88
Gender, number and %			0.46
Female	14 (14%)	1 (6%)	
Male	87 (86%)	17 (94%)	
BMI, kg/m² (mean ± SD)	29.51 ± 8.06	26.27 ± 3.61	0.12
Pre-LT medical problems			
Hypertension			
No	62 (61%)	12 (67%)	0.67
Yes	39 (39%)	6 (33%)	
DM			
No	47 (47%)	5 (28%)	0.14
Yes	54 (53%)	13 (72%)	
HCC before LT	85 (84%)	14 (78%)	
No	16 (16%)	5 (22%)	0.50
Yes			
Vascular complications (PVT) before LT			
No	100 (99%)	18 (100%)	1.000
Yes	1 (1%)	0 (0%)	
Failure of IFN based therapy before LT			
No	63 (62%)	6 (33%)	**0.023**
Yes	38 (38%)	12 (67%)	
Duration between LT and start of DAA	4.4 ± 3.09	6.34 ± 3.52	**0.039**
(mean ± SD), y			
Baseline Labs, units			
Hb, gm/dl	13.8 ± 1.6	13.2 ± 2.0	0.25
WBCs, 10^3/cmm	5.3 ± 1.8	4.5 ± 1.2	0.09
PLT, 10^3/cmm	165 ± 63	148 ± 48	0.3
Total bilirubin, mg/dl	0.98 ± 0.63	1.35 ± 0.93	0.15
Indirect bilirubin	0.55 ± 0.34	0.44 ± 0.22	0.35
AST, U/L	65 ± 53	101 ± 82	0.12
ALT, U/L	81 ± 62	124 ± 129	0.23
ALP, U/L	141 ± 118	242 ± 260	0.23
GGT, U/L	186 ± 267	623 ± 707	0.13
Serum albumin, gm/dl	4.08 ± 0.47	3.61 ± 0.47	0.20
INR	1.05 ± 0.14	1.11 ± 0.09	0.14
Creatinine, mg/dl	1.07 ± 0.29	0.98 ± 0.29	0.274
HbA1c, %	6.7 ± 1.3	6.9 ± 1.6	0.27
Serum AFP, ng/ml	5.4 ± 6.3	16.3 ± 14.8	**0.013**
HCV-RNA post LT(x10^6), IU/ml	4.5 ± 8.1	2.96 ± 3.59	0.44
Complications post LT and before starting DAA treatment			
Acute rejection			
No	89 (88%)	17 (94%)	0.69
Yes	12 (12%)	1 (6%)	
Biliary complications (leak, stenosis)			

(Continues)

TABLE 3 (Continued)

Demographic data	RS (n = 101)	NR (n = 18)	*P*-value
No	80 (79%)	15 (83%)	1.000
Yes	21 (21%)	3 (17%)	
Stage of hepatic fibrosis			
Fibroscan results***			
< F2 (n = 54)	50	4	0.227
≥ F2 (n = 51)	42	9	
Fibrosis stage (METAVIR scoring system) < F2 (n = 15) ≥ F2 (n = 10)			
	12	3	0.57
	10	0	
Immunosuppression:			
Tacrolimus	6.32 ± 2.68	8.20 ± 3.33	0.164

*Bold = statistically significant (< 0.05), **Available Fibroscan results for only 105 patients with a cut off of 8.5Kpa for significant fibrosis (≥ F2).

The most frequent AE was anemia, which was commonly associated with the use of SOF-RBV, 52/190 (27.4%) patients needed RBV dose reduction, while RBV was discontinued in 12/190 (6.3%) received erythropoietin and only one patient needed the blood transfusion.

Transient hyperbilirubinemia developed at week 4 during SOF/SMV therapy in 13 patients (34%) and eventually normalized during the course of treatment despite the continuation of DAAs. Total serum bilirubin levels ranged from 1.5 and 1.8 mg/dl in seven patients, between 1.8 and 2.5 mg/dl in four patients and more than >2.5 mg/dl in two patients.

Mild Acute cellular rejection (ACR) developed in eight patients (4.2%; six patients who received SOF/RBV and two patients in the SOF/SMV regimen). It was diagnosed during follow-up between EOT and 12 weeks post-therapy by mild elevation in the transaminases. It required modification of dose of immunosuppression with no pulse steroids. All of them were in the responders group.

10 | DISCUSSION

With the advent of DAAs, the standard of care for HCV therapy has changed to a combination all-oral IFN-free DAAs. SVR rates with DAA-containing regimens are promising and will eventually lead to a significant reduction in morbidity and mortality; however, experience on post-LT treatment with DAA therapy in real-world cohorts is limited.

The current study was able to demonstrate that the different SOF-based regimens were highly effective and relatively safe for real-world experience for the treatment of recurrent HCV after LDLT in a cohort of difficult-to-treat patients. This study represents the first real-world study addressing the response of DAA therapy in recurrent HCV-G4 post LDLT in Egypt.

All patients with recurrent HCV received and completed a 12 or 24-weeks different SOF-based DAA therapy. The largest cohort (n = 119) received SOF/RBV being the earliest available regimen approved. The Overall SVR12 in the different SOF-based regimens was 89.5% (84.9% in SOF/RBV group, 94.7% in SOF/SMV, 100% in SOF/DCV, and 100% in SOF/LDV) with no statistically significant difference in SVR12 between all groups ($P = 0.104$). Thirteen of the patients who failed SOF-RBV for 24 weeks were given SOF/DAC/RBV 24 weeks and two of them received SOF/LDV/RBV. All of them achieved SVR12 (100%).

SVR12 was achieved in 84.9% with 24 weeks of SOF-RBV therapy which was higher than that achieved in the first study done to evaluate the efficacy of IFN-free therapy in HCV recurrence following LT (70%) as previously reported by Charlton and his colleagues. This difference may be due to the fact that 40% of their patients were cirrhotic and mainly GT1, while in the present study only 34% had advanced fibrosis.[7] Moreover, lower SVR12 rate (39/70; 56%) previously reported by Forns and co-workers[8] was attributed to low life expectancy in their patients owing to the severity of the liver disease and the presence of hepatic failure.

Furthermore, SVR 12 reported in our study after 24 weeks of SOF + RBV therapy was higher than that reported in non-transplant patients. The SVR12 rate was 78.7% in GT4 patients who received the same regimen for a similar duration, of whom 61% had liver cirrhosis.[9] However, our cohort number was much smaller compared to the large number included in this study.

For the SOF/SMV group, SVR12 was achieved in 94.7% (36/38), one patient was nonresponder, while the other one had a viral breakthrough. Similar SVR12 rates of 94% and 95% were in recurrent HCV GT1, post LT who received the same regimen[10]. In addition, our results were comparable to a multicenter study performed by Pungpapong et al[12] on GT1 HCV recurrence post LT. They were treated with SOF/SMV ± RBV for 12 weeks with 90% SVR12. The difference in SVR12 rates could be related to the fact that 82% of their patients had previously failed PEG-IFN/RBV-based regimens and 7% had the kidney transplant.[12] Moreover, a retrospective study on 30 patients with HCV recurrence including 42% of patients had ≥F3 Metavir fibrosis received 12-week of SOF/SMV therapy, 93% (28/30) SVR.[13] Similar results were detected in the COSMOS study on non LT GT1 patients receiving the same regimen for the similar duration with the SVR12 rate 93%.[14]

Regarding SOF/DCV group, SVR12 was 100% (n = 22), although this group had 13 patients who were prior SOF/RBV treatment failure. This in agreement with phase 3 ALLY-1 trial where a 12-week course of SOF/DCV/RBV to treat 53 patients with recurrent HCV post LT achieved an SVR12 of 94%, including 39 (95%) of 41 with genotype 1 HCV infection.[15] Our SVR12 results were higher than those reported by Fontana et al[3] (91%). However, this could be due to 37% included in his study had more severe disease that is, fibrosing cholestatic hepatitis.[3]

SVR12 was 100% among patients who received SOF/LDV (n = 11), two patients were prior SOF/RBV treatment failure. Although the number included was small, these results were in agreement with the Cohort B of the SOLAR-1 trial, treatment-experienced patients with recurrent HCV G1 or 4 (n = 229) who received SOF/LDV plus RBV.[16]

On assessing overall predictors of response, this study showed no statistically significant difference in demographic data between responders and non-responders.

The mean duration between LT and the start of DAAs was 4.50 ± 3.48 years in RS vs 6.79 ± 3.78 years in NR with a significant difference; $P = 0.020$. A similar mean duration (4.5 years) between LT and the start of antiviral therapy was evident among responders to DAA therapy [7] in Charlton's study.

Previous IFN therapy was statistically significant and related to the failure to achieve SVR12. Similarly, Charlton and his colleagues reported 70% SVR12 in a cohort of patients with recurrent HCV where 88% of their patients were IFN-experienced.[7]

Responders had a significantly lower baseline serum AFP than the NR group; on the other hand, the baseline viral load did not show such significance. Comparable results were demonstrated in a recently published study on a cohort of Egyptian HCV non-transplant; SVR12 was achieved among patients who had lower AFP.[9]

The presence of significant hepatic fibrosis > F2 as detected by Transient Elastography was not statistically related to SVR. In contrary, previous studies in transplant and non LT patients,[7,9] had demonstrated the relation between significant hepatic fibrosis and poor response. This could be related to the smaller number of patients with advanced fibrosis included in our study.

No statistically significant difference between different types of immunosuppression in RS and NR groups. The main immunosuppression used was calcineurin inhibitors (tacrolimus in 131 patients [68%] and cyclosporine in 42 patients [22%]), which was similar to the study performed by Charlton and his colleagues.[7]

Regarding the safety of different SOF-based therapy, in general, it was safe and well tolerated. In both SOF/DCV and SOF/LDV, no death, graft loss, or episodes of rejection were noted. No interactions were reported with any immunosuppressant agents.

However, there were complications during the treatment, because of to the use of RBV, hemolytic anemia was the most frequent complication in SOF/RBV group. Despite the slow dose-escalation protocol starting with 200 mg of RBV, 52 patients (27.4%) required RBV dose reductions and 12 patients (6.3%) stopped the RBV and received erythropoietin and only one patient needed the blood transfusion. Although Charlton and his colleagues[7] started with a higher dose of 400 mg RBV orally daily, only one-quarter of their patients required RBV dose reduction and anemia prevented full RBV dosing in the majority of patients.[6] In compassionate use of protease inhibitors in viral C liver (CUPILT) study, the rate of anemia was 72% in patients who received RBV in addition to SOF/SMV versus 5% in those who did not.[12]

One patient in the SOF/RBV group with uncontrolled DM and hypertension and chronic heavy cigarette smoker had MCA infarction (during week 8 of treatment). According to the clinical judgment, this was not related to SOF/RBV used but was mainly driven by his medical comorbidities. His medical record revealed that he was not compliant to his antihypertensive medications and lost follow-up visits in spite of calling him back. No drug interactions between the DAAs used and the antihypertensive medications as the patient was on losartan and bisoprolol. In addition, according to the largest study performed by ElSharkawy et al on Sof/RBV treatment regimen in genotype 4 (number included was 14 409 patients), no such serious adverse event was noted.

Also, transient hyperbilirubinemia starting from the 4th week during treatment was experienced in 13 patients (34%) and eventually normalized during the course of treatment despite the continuation of the DAAs with only 1% (2/190) having bilirubin >2.5 mg/dl. This was in agreement with Pungpapong et al[12] who reported that 2% of the patients had hyperbilirubinemia > 3 mg/dl. On the contrary, the study performed by Punzalan et al[11] used a similar regimen for the similar duration, in which no one experienced hyperbilirubinemia.

Mild ACR reported in eight patients post-treatment (4.2%; six patients who received SOF/RBV and two patients in the SOF/SMV regimen). It required modification of dose of immunosuppression with no pulse steroids. All of them were in responders.

The present study showed that one patient who was transplanted for HCC outside Milan criteria, had HCC recurrence at week 8 post-treatment with a 12-week regimen of SOF/SMV with lymph nodes and bone metastases and eventually died. This HCC recurrence and death could be linked more to his pretransplant advanced tumor. However, the issue of increased incidence of liver cancer after successful DAA treatment of chronic hepatitis C is controversial. It was, therefore, a cause of great concern that the publication of two reports suggesting the treatment with DAAs could increase the risk of HCC in cirrhotic patients. These reports have generated a great and controversial debate and have been followed by a series of publications not confirming such increased risk. In the CO23 CUPILT cohort, including 314 patients undergoing liver transplant for HCV related HCC, HCC recurrence was seen in only 2.2% of the cases during a follow-up of 7 ± 3 months after antiviral therapy. The Authors concluded that there was no evidence of an increased risk of HCC recurrence in patients treated with DAAs. It should be outlined that most published studies reported HCC recurrence with DAA in the range of what is expected in the natural course of the disease.[17] Rates of HCC recurrence after DAAs were extremely variable in different studies.[17] The possibility that treatment with DAAs may favor tumor growth and spread in

individual patients with active HCC foci is suggested by some observations but remains unproven. The ongoing debate makes it difficult in this case to suggest a relationship to treatment, and this could remain a possibility.

De-novo HCC occurred in a male cirrhotic patient who was transplanted in 2004 and was prior SOF/RBV relapser post LT. HCC developed after achieving SVR12 following SOF/DCV/RBV regimen for 6 months for which he had a resection. The development of HCC could be explained as a part of the natural course of HCC occurrence in patients with liver cirrhosis particularly those under immunosuppression. This is matching with most available reports about "de novo" occurrence of HCC in cirrhotic patients treated with DAAs in the absence of previous HCC, that agree on the conclusion that risk is not increased by treatment compared to what is expected in untreated patients.[17] Accordingly and mimicking the natural history of the disease, the residual risk of HCC occurrence during/after DAAs is dependent on stage of liver disease and cofactors and comorbidities known to affect HCC risk in hepatitis C.[17] Data on "de novo" HCC incidence suggest that treatment with DAAs is not modifying the risk of developing HCC in the first 6 to 12 months.[17]

Finally, this study was conducted with a variable number of patients in each DAA regimen, potentially limiting the generalizability of the findings. Most patients had minimal post-LT liver disease, which is not representative of all HCV-infected LT recipients who are characterized by an aggressive progression of HCV infection post-LT or advanced fibrosis. In addition, our cohort demonstrated generally excellent medication adherence and follow-up. These factors combined with intensive multidisciplinary patient care likely contributed to our observed DAA treatment success.

11 | CONCLUSION

Different Sofosbuvir-based regimens were effective with high SVR12 rates and relatively safe in a difficult-to-treat unique population, recurrent HCV post LDLT.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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