The Egyptian Journal of Hospital Medicine (April 2022) Vol. 87, Page 973-978

Safety and Efficacy of Sofosbuvir Based Regimens in the Treatment of HCV Recurrence Post Liver Transplantation

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ABSTRACT

Background: Hepatitis C virus (HCV) recurrence after liver transplantation (LT) is universal and associated with an accelerated disease course. Second-generation direct-acting antivirals dramatically improve viral clearance. Their use in the Egyptian population in the post-transplant setting needs further evaluation.

Objectives: To evaluate the safety and efficacy of sofosbuvir-based regimens in the treatment of HCV recurrence after LT in the Egyptian population.

Patients and methods: Sixty patients with HCV recurrence after LT were included. Twenty patients received sofosbuvir (SOF) in combination with ribavirin (RBV) for 24 weeks, 21 patients received SOF and simeprevir (SIM) for 12 weeks and 19 patients received SOF and daclatasvir (DCV) with or without RBV for 12 or 24 weeks according to the stage of liver fibrosis and eligibility for ribavirin. Treatment response and adverse events were analyzed.

Results: The mean age was 52.5±7.9 years. Most of patients were males (91.7%). Sustained virological response at week 12 after treatment (SVR12) was achieved in all patients who received SIM/SOF and SOF/DCV±RBV regimens and in 85% of patients who received SOF/RBV regimen. The most common reported adverse events were fatigue, anemia and hyperbilirubinemia. Fatigue was reported in 75% of patients in SOF/RBV group and in 85.7% of patients in SIM/SOF group. Anemia was reported in 15, 4.8 and 10.5% of patients in SOF/RBV, SIM/SOF and SOF/DCV±RBV groups respectively, whereas hyperbilirubinemia was documented in 10% of patients in SOF/SIM group and in 9.5% of patients in SIM/SOF group.

Conclusion: Sofosbuvir-based combinations are safe and effective in the treatment of recurrent HCV after LT, especially when combined with another directly acting antiviral.

Keywords: DAAs, Daclatasvir, Recurrent HCV after liver transplantation, Simeprevir, Sofosbuvir.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection and its related complications are among the most common indications for liver transplantation worldwide [(1)]. HCV viraemic prevalence was estimated to be 7.3% in Egypt. Because of such a high prevalence, HCV is considered the leading cause of liver transplantation in Egypt [(2)].

Hepatitis C virus recurrence after liver transplantation (LT) is universal and associated with a relatively progressive disease course; graft fibrosis, cirrhosis and decompensated liver disease [(3,4)]. Unfortunately, HCV recurrence post liver transplantation significantly affects patient survival, with an estimated survival rate of less than 10% at 3 years [(5)]. Accelerated advances in direct-acting antivirals (DAAs) in the last few years have increased the success rate of HCV eradication considerably and significantly improved the outcome of hepatitis C therapy with a positive impact on both graft and patient survival [(6)].

Recent studies have shown that LT recipients can be safely and effectively treated with DAA combination therapies. These agents offered treatment of HCV recurrence post LT with an all-oral regimen for short duration, with few adverse effects and high cure rates [(7)].

The current study aimed to evaluate the safety and efficacy of sofosbuvir-based regimens in the treatment of HCV recurrence after liver transplantation in the Egyptian population.

PATIENTS AND METHODS

The current study was conducted on patients who received living donor liver transplantation for HCV-related decompensated liver cirrhosis at the National Liver Institute, Menoufia University, Egypt, and who developed recurrent HCV infection after the transplant. Recurrent HCV infection was defined as positivity of serum HCV RNA after liver transplantation.

Pediatric and young adult recipients below 18 years were ruled out. From December 2014 to September 2017, sixty eligible patients were enrolled and started on sofosbuvir (SOF)-based antiviral medications regardless of their pre-transplant treatment status, whether treatment naïve or experienced. At least 3 months should have elapsed after liver transplantation to start treatment.

Received: 10/12/2021
Accepted: 28/01/2022

Prior to treatment, all eligible patients were subjected to thorough medical history taking, complete physical examination, abdominal ultrasonography, liver stiffness measurement (LSM) by FibroScan (Echosens, Paris, France) and laboratory tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, serum albumin, INR, complete blood count, Alfa-fetoprotein (AFP), fasting, blood glucose (FBG), glycated hemoglobin (HbA1c) for diabetic patients, blood urea, and serum creatinine in addition to hepatitis B serology and HCV RNA.

Treatment regimens:

Three oral SOF-based regimens were used:

1. **SOF plus ribavirin** (RBV) for 24 weeks.
2. **SOF plus simeprevir** (SIM) for 12 weeks. This regimen was given only to patients on tacrolimus or rapamune based immunosuppression
3. **SOF plus daclatasvir** (DCV) for 12 weeks when liver fibrosis was ≤ F2, which is equivalent to a LSM of < 9.5 kPa by FibroScan. SOF/DCV+RBV regimen was given for 12 weeks to patients with liver fibrosis > F2 (LSM ≥ 9.5 kPa) and who were eligible to receive RBV. In patients who were RBV ineligible, SOF/DCV regimen was given for 24 weeks.

All medications were given orally as a daily dose of 400 mg for SOF, 150 mg for SIM and 60 mg for DCV.

In SOF/RBV group, ribavirin was started as a daily dose of 200 mg and increased by 200 mg weekly guided by hemoglobin level, with a maximum daily dose of 1000 mg for patients below 75 kg and 1200 mg for those equal to or more than 75 kg.

In SOF/DCV±RBV group, the initial daily dose of ribavirin was 600 mg and increased gradually, if tolerated, to 1000 mg. RBV dose was gradually reduced if hemoglobin level dropped below 10 mg/dl and discontinued if hemoglobin level went further below 8 mg/dl.

On treatment, serial HCV RNA testing was done at weeks 4, 8, 12 and 24. Patients with undetectable HCV RNA at the end of treatment underwent further HCV RNA testing at week 12 post-treatment to evaluate sustained virological response (SVR).

Efficacy evaluation:

Treatment efficacy was evaluated by:

a) Rapid virological response (RVR), defined as HCV RNA below the lower limit of quantification (LLOQ) at week 4 of treatment.

b) End of treatment (EOT) response, defined as HCV RNA below LLOQ at the end of treatment.

c) Sustained virological response (SVR), defined as HCV RNA below LLOQ at week 12 post-treatment.

Treatment failure was defined as failure to achieve ETR or reappearance of HCV RNA at week 12 post-treatment after being negative at the end of treatment.

Safety evaluation:

Safety of the used medications was assessed by close observation of patients for any drug-related adverse events occurring during treatment and up to 12 weeks post-treatment, including minor events or major ones necessitating hospitalization, cessation of therapy or even death.

Ethical consideration:

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans and has been approved by Institutional Review Board of National Liver Institute, Menoufia University, Egypt. All patients provided an informed written consent before enrollment.

Statistical analysis

Data were collected, tabulated and statistically analyzed using an IBM personal computer with Statistical Package for the Social Sciences (SPSS) version 20 for Windows (Inc, Chicago, IL, USA). Quantitative data were presented in the form of mean and standard deviation, while qualitative data were presented as numbers and percentages. Graphs were developed using Microsoft Excel 2013 software. The statistical significance was set at P-value of less than 0.05.

RESULTS

The baseline characteristics of the studied patients are shown in table 1.

Table (1): Baseline characteristics of the studied patients

Data	Mean±SD, n (%)
Age (years)	52.38±7.9
BMI (kg/m^2)	29.23±4.52
Gender • Males • Females	 55 (91.7) 5 (8.3%)
Pre-transplant Hypertension	10 (16.7)
Pre- transplant DM	23 (38.3)
Treatment naïve	52 (86.7)
Treatment experienced	8 (13.3)
Time interval between LT and DAAs (months)	40.9 ± 31.9
Bilirubin (mg/dl)	0.88±0.19
Albumin (g/dl)	4.1±0.46
ALT (IU/l)	54±3
AST (IU/l)	47±3
AFP (ng/ml)	7.76±1.19
Hemoglobin (g/dl)	13.9±2.4
WBCs (x10^3/mm^3)	5.1±1.8
Platelets (x10^3/mm^3)	150.1±6.1
INR	1.09±0.15
Creatinine (mg/dl)	0.95±0.25
HbA1c (%)	6.3±1.2
HCV RNA ×10^6 (IU/ml)	3.65±0.6
Liver stiffness measurement • ≤ F2 • > F2	 49 (81.7) 11 (18.3)
Immunosuppressive drugs	
Calcineurin inhibitors: • Tacrolimus • Cyclosporine mTOR inhibitors: • Sirolimus • Everolimus Antiproliferative drugs: • Mycophenolate mofetil • Mycophenolate sodium	 46 (76.7) 4 (6.7) 8 (13.3) 2 (3.3) 26 (43.3) 13 (21.7)

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAAs, direct acting antiviral agents; AFP, alpha fetoprotein; WBCs, white blood count; HbA1c, glycated hemoglobin; HCV RNA, hepatitis C virus ribonucleic acid; INR, international normalized ratio.

Twenty patients received the SOF/RBV regimen for 24 weeks, 21 patients received the SOF/SIM regimen for 12 weeks, 14 patients received the SOF/DCV regimen for 12 weeks, 3 patients received the SOF/DCV/RBV regimen for 12 weeks and 2 patients, who were RBV ineligible, received the SOF/DCV regimen for 24 weeks.

Rapid virological response (RVR) was achieved in 90, 81 and 84.2% of patients in the SOF/RBV, SOF/SIM and SOF/DCV±RBV regimens respectively.

There was no significant statistical difference between the groups (P = 0.180) as regard end-of-treatment (EOT) response (Table 2 and figure 1).

Table (2): Treatment outcomes

Treatment response	SOF/RBV 24 w n=20	SOF/SIM 12 w n=21	SOF/DCV ± RBV 12-24 w n=19
Undetectable HCV RNA			
– Week 4 (RVR)	18 (90%)	17 (81%)	16 (84.2%)
– Week 8	19 (95%)	21 (100%)	19 (100%)
– EOT	20 (100%)	21 (100%)	19 (100%)
– Week 12 after treatment (SVR-12)	17 (85%)	21 (100%)	19 (100%)
Positive HCV RNA at week 12 post treatment			
– Treatment failure	3 (15%)	0 (0%)	0 (0%)

w, week; SOF, sofosbuvir; RBV, ribavirin; SIM, simeprevir; DCV, daclatasvir; EOT, end of treatment; RVR rapid virological response; EOT, end of treatment; SVR, sustained virological response.

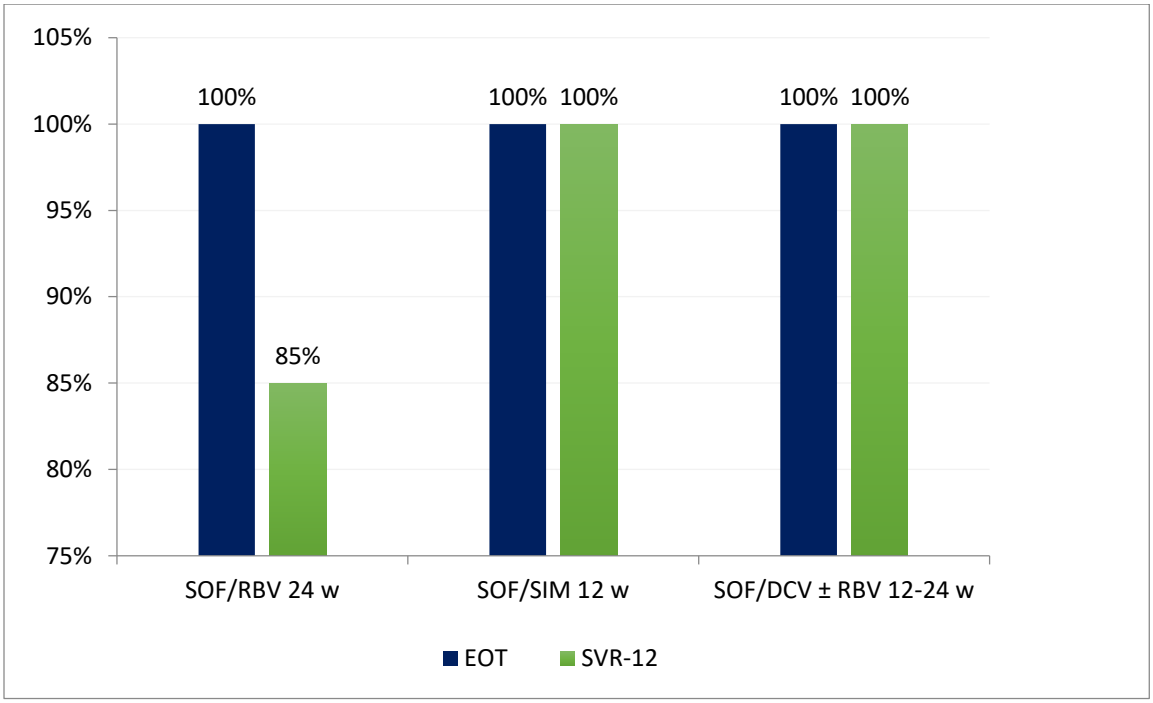

Figure (1): Treatment response

SOF, sofosbuvir; RBV, ribavirin; w, week; SIM, simeprevir; DCV, daclatasvir; EOT, end of treatment; EOT, end of treatment; SVR, sustained virological response.

All used regimens were well tolerated, with no serious adverse events necessitating hospitalization or treatment discontinuation. The reported adverse events are demonstrated in figure (2). Fatigue was the most common adverse event followed by anemia.

Anemia was reversed in the five patients who were receiving RBV after a reduction in its dose. In the one patient who was receiving the SOF/SIM, anemia was mild (hemoglobin 9.8-10.3 gm/dl) during treatment and increased to over 11 gm/dl after completion of therapy.

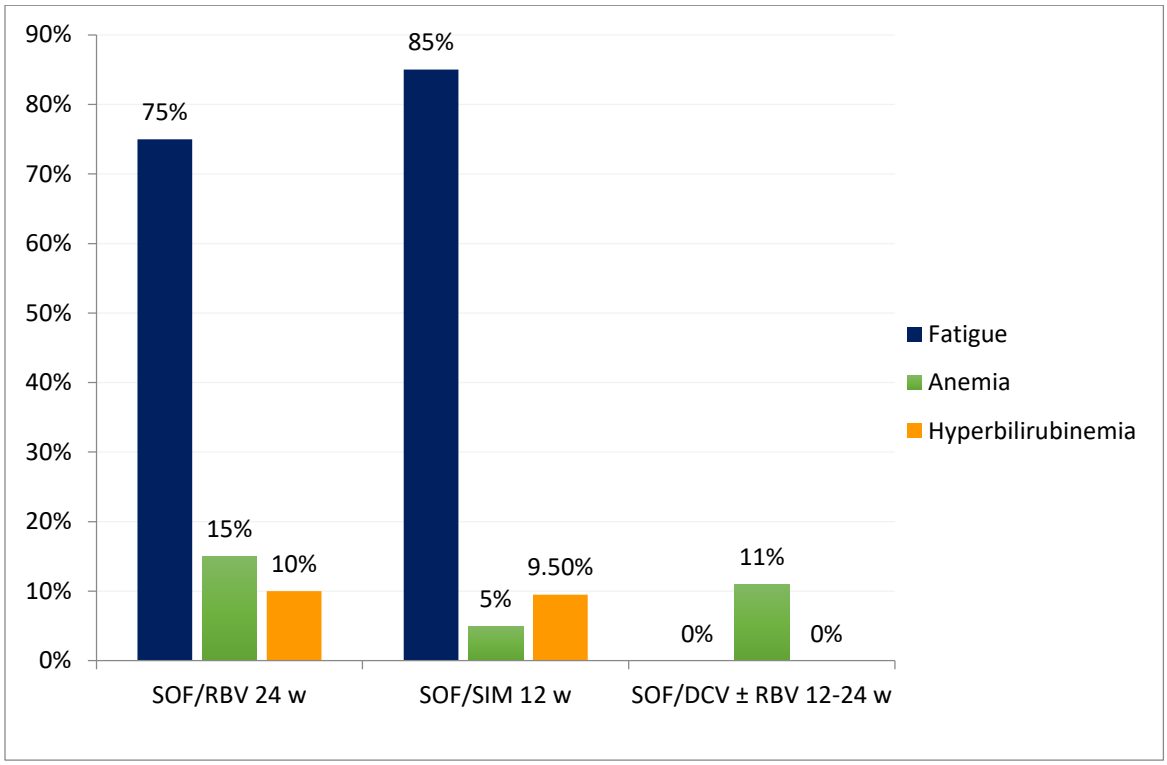

Figure (2): The most common reported adverse events
SOF, sofosbuvir; RBV, ribavirin; SIM, simeprevir; DCV, daclatasvir

DISCUSSION

The introduction of direct-acting antiviral agents as an effective treatment of HCV chronic infection has dramatically altered the landscape of antiviral therapy. DAAs are being used in different populations of HCV-infected patients, including liver transplant recipients [(5)].

In the current study, all patients achieved an end-of-treatment response. With the SIM/SOF and SOF/DCVRBV combinations, the sustained virological response (SVR12) was 100%. **Charlton and his colleagues** used sofosbuvir after liver transplantation to treat 40 patients with recurrent HCV. The SVR was 70%, which was lower than our results. This may be explained by the fact that 88% of the patients were interferon-experienced, and 40% of these patients started HCV treatment late after transplantation, when liver cirrhosis had already been established. As regards complications, **Charlton and his colleagues** reported that the most common adverse events were fatigue (30%), diarrhea (28%), headache (25%) and anemia (20%) [(8)].

Another study done by **Khemichian and colleagues** [(9)] evaluated post-liver transplant patients with genotype 1 HCV recurrence. All patients with advanced fibrosis (F3) or cirrhosis (F4) were treated with simeprevir and sofosbuvir for 12 weeks. The SVR12 rate was 94%. This rate of response is lower when compared to our results. This could be explained by the advanced stage of fibrosis in this cohort as well as the genotype I, which represents a challenging group of patients to treat.

Our results were similar to a cohort published by **Nair and colleagues** [(10)]. They treated fifty consecutive patients with recurrent hepatitis C genotype 1 with standard doses of simeprevir and sofosbuvir for 12 weeks. Ribavirin was adjusted based on hemoglobin levels. All patients achieved a sustained virologic response. Overall, the antiviral treatment was well tolerated, with no reported interactions with immunosuppressive drugs or complications.

Saab and colleagues [(11)] treated 26 patients using sofosbuvir with simeprevir. The mean time from liver transplant to the initiation of treatment was 71.8 ±77.1 months. The SVR was 93%. All recipients were able to complete therapy and no patients required growth factors or blood product transfusions during treatment. No patient required drug interruption of their immunosuppressive therapy. Similar results were achieved by many other researchers with no significant complications [(12-14)].

In our study, SVR12 was 100% among patients who received SOF/LDV (n = 21). These results were in agreement with the cohort done by **Poordad and his**

colleagues [15]. In their study, 12 weeks of treatment with the pan-genotypic combination of daclatasvir with sofosbuvir and ribavirin achieved SVR12 rates of 94% in post-transplantation HCV recurrence. The regimen was effective across all five HCV genotypes enrolled without any significant complications.

In the same context, sofosbuvir and daclatasvir with or without ribavirin were used in a French prospective multicenter cohort to treat 137 post-liver transplant patients with recurrent HCV. The rate of SVR-12 was 96%. Serious adverse events were reported in 17.5%. Anemia was the most common adverse event, with significantly more cases in the ribavirin group. Four patients (3%) prematurely stopped treatment because of serious adverse events. There was no clinically relevant drug-drug interaction however modifications or change of immunosuppressive medications were required in 52% of patients [16].

Our study has limitations. First, the cohort was from a retrospective, single center experience; however, our center is the first to do living donor liver transplants in Egypt, with a large pool of post-liver transplant HCV recurrence being followed.

Another limitation was the small number of patients. In addition, the study was restricted to a limited number of DAA regimens and did not include the newer antiviral regimens. This is because the regimens used in the current study were the only ones available and approved by the National Egyptian Committee for the Treatment of HCV at the time of the study. The newer regimens have emerged later.

CONCLUSION

Sofosbuvir-based combinations are effective in the treatment of recurrent HCV after liver transplantation in our population and well tolerated with minimal adverse effects.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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