Safety and Efficacy of Sofosbuvir Based Regimens in Treating Chronic Hepatitis C Virus in Egyptian Patients: Real World Study: Single Center Experience

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Backgroundand study aims: Hepatitis C virus (HCV) is the main leading cause of liver disease in Egypt. A new era of HCV treatment has been started with the evolution of direct acting antiviral agents. Sofosbuvir (SOF)-based therapy was introduced by the Egyptian ministry of health in 2014 in an attempt to decrease disease burden. We aimed to evaluate efficacy and safety of Sofosbuvir-based regimens in HCV Egyptian patients with compensated liver disease.

Patients and Method: This study was conducted in National Liver Institute, MenoufiaUniversity, Egypt. Seven hundred patients out of seven hundred fifty-eight chronic HCV patients with compensated liver disease who met the inclusion criteria were included. According to treatment regimen patients were divided to 4 groups; group 1 received Sofosbuvir (SOF), Pegylated interferon (PEG-IFN) plus ribavirin (RBV), group 2 received SOF plus RBV, group 3 received SOF and Simeprevir± RBV, group 4 received SOF and Daclatasvir ±RBV.

Results: The overall SVR was 90.9%, 81.5%, 95% and 98% in groups 1, 2, 3, and 4 respectively. SVR in patients with liver cirrhosis was 90.56, 79.16, 95 and 96% in the 4 groups respectively. In treatment experienced patients, SVR was 86.8% in group 1, 78.3% in group 2, 100% in group 3 and 86.7% in group 4.

Conclusion: Sofosbuvir plus daclatasvir with or without ribavirin is the safest andmost effective SOF-based regimen in treatment of HCV Egyptian patients with compensated liver disease.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is one of the most important clinical and public health problems. In 2015, the Center for Disease Control (CDC) estimated that 170 million people worldwide are chronically infected with HCV [1]. Although about 20% of infected individuals spontaneously clear the virus without treatment, approximately 80% will develop chronic HCV infection[1].

The major burden of HCV infection comes from sequelae following the chronic infection. Because patients with chronic infection are at risk of developing liver diseases including cirrhosis and liver cancer, with 350,000 annual deaths due to all HCV-related causes [2].

The standard of care to treat HCV infection was injection of pegylated interferon (PEG-IFN) and daily ribavirin. This regimen was expensive, toxic, complicated to deliver and its cure rates were less than 50%, especially for people with cirrhosis [3]. Now, most people can be cured of HCV infection with the new oral direct-acting antivirals DAAs; that target different steps of the lifecycle of HCV. Numerous clinical trials and clinical practice have shown thatDAAs are very effective and well tolerated[4].

In 2011, the first-generation of DAAs was introduced with two drugs boceprevir and telaprevir. Later, in 2013, approval of the second-generation DAA, NS5B polymerase inhibitor sofosbuvir (SOF), has been a further step forward. Sofosbuvir has pan-genotypic effect on HCV with better pharmacokinetics and improved resistance profiles [5]. Sofosbuvir based DAAs are safe, effective, and well tolerated in patients with chronic hepatitis C patients [6].

In the current study we aimed to evaluate the safety and efficacy of different Sofosbuvir (SOF) based regimens among Egyptian patients with compensated HCV related chronic liver disease.

PATIENTS AND METHODS

At national liver institute, Menoufia, Egypt, 758 patients with HCV related compensated liver disease have been enrolled in the present study in the period between 2015 to 2016. Patients included in the current study were HCV compensated liver diseases. HCV was diagnosed by positivity for both HCV antibody and HCV RNA by PCR.

Patients were divided into 4 groups according to treatment regimen applied for each group; group 1 received SOF, PEG-IFN plus RBV for 12 weeks, group 2 received SOF plus RBV for 24 weeks, group 3 received SOF and Simeprevir (SIM) with or without RBV for 12-24 weeks according to the state of fibrosis (presence or absence of cirrhosis) and treatment status (naïve or experienced), group 4 SOF and Daclatasvir with or without RBV for 12-24 weeks according to the state of fibrosis and treatment status. The selection of patients for each group followed the national guidelines during the study period as well as availability of the given medications.

Dosing of the used medications were scaled as the following; PEG-IFN, 1000 μg subcutaneously once weekly, RBV, 1200 mg/day for those equal or more than 75 kg body weight and 1000 mg/ day for those weighing less than 75 kg, SOF, 400 mg once daily, SIM, 150 mg once daily and daclatasvir 60 mg once daily.

Transient elastography (FibroScan) has been used to evaluate the state of fibrosis; F1 was considered if reading was less than 7.0 kPa, F2 was considered if reading ranged between 7.0 and 9.5 kPa, while F3 was considered if reading

was equal or higher than 9.5 kPa and less than 12.0 kPa and finally F4 was considered if reading was equal or higher than 12.0 kPa.

Patients were subjected to full laboratory panel, conventional abdominal ultrasonography and Child Turcotte Pugh (CTP) score was calculated for each patient. Diagnosis of cirrhosis based on clinical, laboratory, ultrasonic as well as FibroScan findings (and biopsy results if available).

Patients with CTP more than 8, bilirubin more than 3.0 mg/dl, or impaired kidney functions with estimated glomerular filtration rate (eGFR) less than 30 ml/min were ruled out. Patients co-infected with HBV or HIV were also excluded.

Active hepatocellular carcinoma (HCC) or recently treated HCC of less than 4 weeks elapsed after successful treatment has been ruled out. Active extrahepatic malignancy or treated patients who did not reach at least 2 years of disease-free survival have been also excluded.

Negative HCV RNA12 weeks after end of treatment (SVR12) was the end point used to assess treatment efficacy. All adverse events have been reported in each group.

Ethics approval and consent to participate

The study was approved by the ethics committee of National Liver Institute (NLI), Menoufia University. A signed written informed consent was taken from all patients before participation in the study.

Statistical analysis methods

SPSS, version 20 for windows (Inc, Chicago, IL, USA) was used for all statistical analyses. Qualitative data were presented as frequency and percentage. Chi square and Fisher's exact tests were used to compare groups. Quantitative data were presented as mean and standard deviation. Student t-test and Wilcoxon rank-sum test were used to compare non- parametric data. The statistical significance was set at P-value of less than 0.05 for all tests.

RESULTS

Fifty-eight patients did not fulfill the inclusion criteria, so 700 out of 758 patients were only included; group 1 included 159 patients, group 2 included 138 patients, group 3 included 201 patients and group 4 included 202 patients.

The mean age was 49.36±9.19, 54.58±9.28, 49.46±11.4 and 50.25±10.8 years in group 1, 2, 3 and 4 respectively. The baseline data of the studied patients are shown in table 1. In the current study 156 patients were compensated cirrhosis, while 544 patients were non-cirrhotic.

Previous HCV treatment with IFN or peginterferon (PEG) associated with ribavirin (RIB) was recorded for 116 (16.6%) patients, the remaining patients 584(83.4%) had not been previously treated.

The overall SVR in group 1 was 90.97% with a quite similar rate among cirrhotic patients (90.56%) and a slightly lower rate in treatment experienced patients (86.8%). In group 2, SVR was 81.5% with slightly lower rates among cirrhotic and treatment experienced patients; 79.16 and 78.3% respectively. In group 3, SVR was similar to the overall SVR; 95 and 95.5% respectively. Surprisingly it was 100% in treatment experienced patients. In group 4, the overall SVR was 98% with slightly lower rates among cirrhotic (96%) while in treatment experienced patients it dropped down to 86.7%.

The overall SVR and SVR in difficult to treat patients (cirrhotic and treatment experienced) in the studied groups are shown in figure 1.
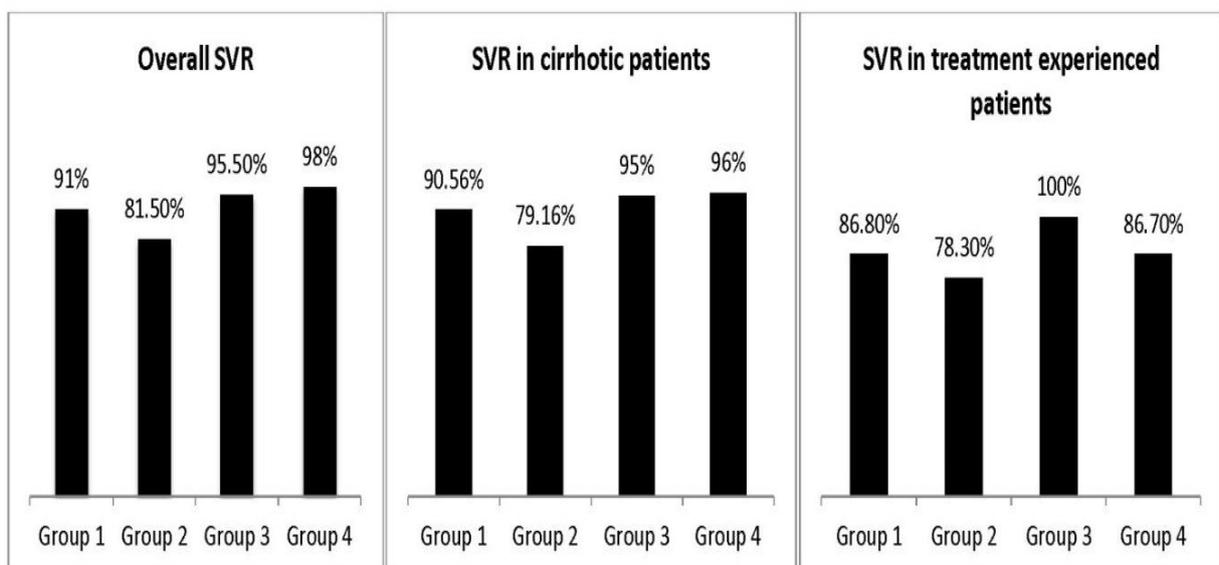
The overall SVR was significantly different among the studied groups (p<0.001) with highest rate in group 4. Similarly, SVR in cirrhotic patients was significantly different among the studied groups (p<0.001) with highest rate in group 4. Finally, SVR in treatment experienced patients was significantly different among the studied groups (p<0.001) with highest rate in group 3.

Adverse events were reported in 89 (55.97%), 82 (59.42%), 88 (40.79%) and 19 (9.4%) in group 1, 2, 3 and 4 respectively. The rate of adverse events was significantly different among the studied groups (p<0.001) with lowest rate in group 4. The most common reported adverse events in group 1 were flu like illness (15.1%) and anemia (12.6%). In group2, anemia and hyperbilirubinemia were the most frequent side effects; 18.8 and 18.1% respectively. In group 3, hyperbilirubinemia and fatigue were the main adverse events; 11.9 and 6.5% respectively. In group 4, only two adverse events have been reported; hyperbilirubinemia (5.9%) and anemia (3.5%).

Reported adverse events in the studied groups are depicted in figure 2

Table (1): Baseline data of the studied patients.

		Group 1 (n= 159)	Group 2 (n= 138)	Group 3 (n= 201)	Group 4 (n= 202)	P value
Age (years)	Range	21-60	22-70	18-70	19-70	
	mean± SD	49.36 ± 9.19	54.58 ± 9.28	49.46 ± 11.40	50.25 ± 10.8	0.564
Sex	Males N (%)	133 (83.6)	106 (76.8)	152 (75.6)	127 (62.9)	0.047
	Females N (%)	26 (16.4)	32 (23.2)	49 (24.4)	75 (37.1)	0.024
Treatment status	Naïve N (%)	120 (75.5)	114 (82.6)	163 (81.1)	187 (92.6)	0.030
	Experienced N (%)	39 (24.5)	24 (17.4)	38 (18.9)	15 (7.4)	0.642
Fibrosis stage (Fibroscan)	F0-2 N (%)	49 (30.8)	15 (10.9)	99 (49.3)	101 (50)	0.010
	F3-4 N (%)	110 (69.2)	123 (89.1)	102 (50.7)	101 (50)	0.441
	Cirrhotic liver	32 (20.1)	41 (28.9)	44 (21.8)	39 (19.3)	0.092
Laboratory data						
AST (U/L)		56.81±41.6	71.61±48.02	54.85±36.9	59.8±39.5	0.180
ALT (U/ml)		71.03±70.8	64.7±44.21	57.15±38.9	64.4±45.6	0.410
Total bilirubin (mg/dl)		0.77±0.27	1.05±0.56	0.82±0.44	0.92±0.52	0.332
Albumin (g/L)		4.25±0.45	3.8±0.51	4.13±0.56	4.01±0.55	0.630
Creatinine (mg/dl)		0.85±019	0.84±0.21	0.84±0.18	0.85±0.19	0.882
INR		0.9±0.27	1.0±0.15	0.9±0.3	0.95±0.1	0.738
Hb (g/dl)		14.74±1.57	13.66±1.81	14.09±1.86	13.56±1.7	0.692
WBC's (C/mm^3)		6.89±2.0	5.57±1.89	6.61±2.28	5.99±1.93	0.584
Platelets (C/mm^3)		198.7±46.5	122.27±55.1	181±67.09	188±77.8	0.039
HCV RNA (IU/ml)		1724399±3086862	1155007±2968751	1678010±2415389	1468920±2494531	0.028

Figure (1): The overall SVR and SVR in cirrhotic and treatment experienced patients.
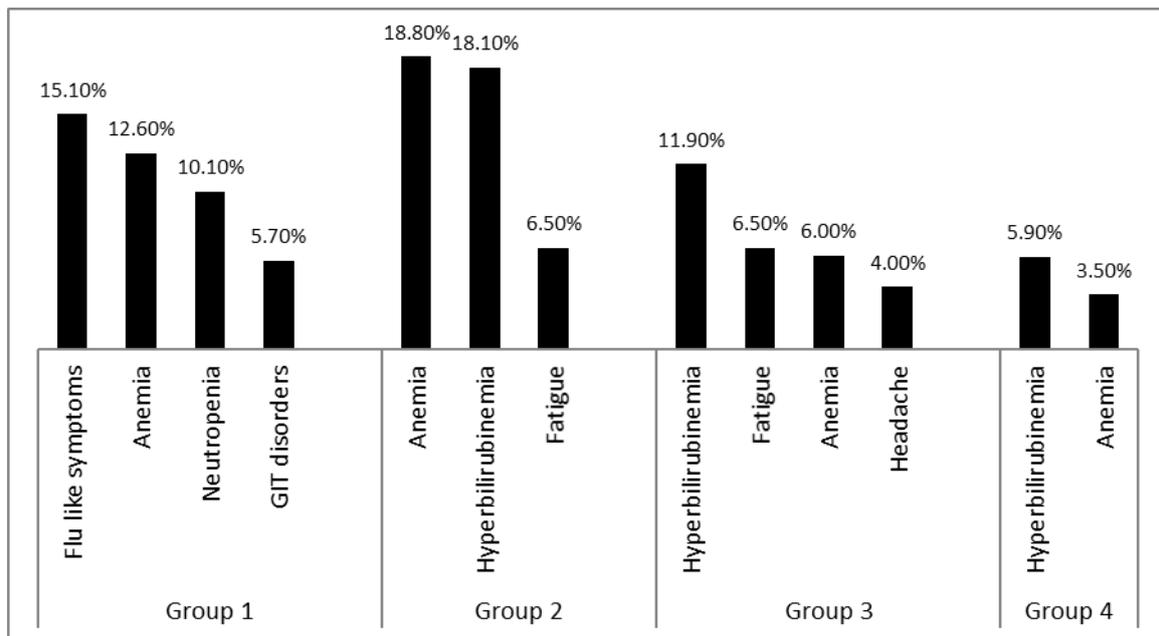
Figure (2): The reported adverse events in the studied groups.

DISCUSSION

HCV is a leading cause of chronic liver disease worldwide and a major health burden [7]. HCV affects approximately 170–180 million people (2–3% of the global population) [8].Due to the widespread schistosomiasis treatment campaigns, Egypt has the highest HCV prevalence in the world, reaching 12% [9].

The main goal of chronic hepatitis C therapy is to eradicate the virus, characterized by sustained virological response (SVR), with subsequent decrease of the liver damage and HCV transmission [10].

The previous standard treatment for chronic hepatitis C (CHC) patients, comprising a combination of PEG-IFN and ribavirin, was associated with severe adverse reactions and suboptimal efficacy [11].

The use of DAAs represents a major advance in CHC therapy, including advances in patients who are intolerant and/or refractory to interferon. The association of DAAs showed SVR rates between 80 and 100% depending ongenotype, previous treatment of CHC and the presence of cirrhosis [12]. Sofosbuviris a selective, pan-genotypic nucleotide inhibitor of NS5B-directed HCV RNA replication. SOF based treatment was proved to be safe and well tolerated in clinical trials [13,14].

Thus, in this study, we aimed to study initial virological response to SOF based treatment regimens (SOF, RBV and Peg IFN-α/SOF and RBV alone/ SOF and Simeprevir/ SOF and Daclatasvir) and describe important real-life data from 700 patients.

In this study the overall SVR in group 1 who received SOF, PEG-IFN plus RBV for 12 weeks was 90.97% with a quite similar rate among cirrhotic patients (90.56%) and a slightly lower rate in treatment experienced patients (86.8%).

These results are similar to that of Lawitz et al [15],who found overall rate of SVR of 89% in HCV patients who received Sofosbuvir with peginterferon-ribavirin

But it is higher than that reported by Wehmeyer et al [16],who found thatSVR12 SOF/Pegylated interferon/Ribavirin in patients infected with HCV genotype 3 to be 80.6% in treatment naïve patients, 81.0% in cirrhotic patients and 80.8% in treatment experienced patients.

In this study the lowest overall response rate was in group 2 patients who received SOF plus RBV for 24 weeks. SVR was 81.5% with slightly lower rates among cirrhotic and treatment experienced patients; 79.16 and 78.3% respectively. In another study from Egypt using sofosbuvir and ribavirin for treatment of CHC infection, the SVR12 was 88.6% in treatment naïve patients and 76.7% in treatment experienced patients. This study also mentioned that, patients with cirrhosis had lower rates of SVR12 than those without cirrhosis (75% versus 89.7%) [17].

Indeed, the combination of interferon and ribavirin with sofosbuvir in treatment of HCV in this study was based on guidelines for treatment of genotype 4 HCV issued in 2014 by the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), and World Health Organization (WHO) which included sofosbuvir administered in combination with Peg-IFNα and RBV for 12 weeks or an interferon-free regimen of sofosbuvir in combination with RBV for 24 weeks [18-20].

In 2018 and onwards, the situation has been changed. Interferon-free, ribavirin free, DAA-based regimens became the best options in HCV-infected patients without cirrhosis (and in those with compensated cirrhosis), including ''treatment-naïve'' patients and ''treatment-experienced'' patients [20].

The National Committee for Control of Viral Hepatitis (NCCVH, Cairo, Egypt) program discontinued interferon-based therapy and introduced interferon-free all-oral treatment protocols, incorporating DAAs from different classes.

IFN-free regimens are becoming the new standard of care for CHC patients and on the other hand, combination of sofosbuvir plus ribavirin alone is no more recommended in by current guidelines because of frequent side effects of ribavirin and somewhat lower SVR rate than other DAAs combinations [21].

In group 3 patients, who received SOF and Simeprevir with or without RBV for 12-24 weeks, the SVR was; 95%, while in cirrhotic patients it was 95.5%. Surprisingly it was 100% in treatment experienced patients.

These results are near to that obtained by Yosry et al[6], who found that, SVR12 was achieved in 94.7% in patients who received SOF/SMV for treatment of hepatitis C virus recurrence post living donor liver transplant.

Indeed, the highest overall SVR in this study was seen in group 4, who were given SOF and Daclatasvir with or without RBV for 12–24.The overall SVR was 98% with slightly lower rates among cirrhotic (96%) while in treatment experienced patients (86.7%).

These results are similar to that obtained by other studies as Yosry et al. [6], Ahmed et al.[22], and Omar et al [23],who found SVR12 in Egyptian patients treated with Sofosbuvir plus Daclatasvir to be 100%, 96% and 95.4% respectively.

The SVR in patients with cirrhosis in group 3 was 95% and group 4 was 96% in our study. These rates are higher than that reported by Kutala et al [24], (73%) as well as those reported in OPTIMIST-2 [25]and ALLY-3 [26] clinical trials.

The highestSVR rateswere achieved in patients who received SOF/DCV±RBV andthosewho received SOF/SIM±RBV. This is in agree with Babatin et al [27], who mentioned that SMV/SOF or DCV/SOF combinations are safe and highly effective in HCV genotype 4 treatment Pearlman et al [28], also found that a regimen of Simeprevir and sofosbuvir produced a significantly higher rate of SVR and was better tolerated, with a lower viral relapse rate, than a regimen of peginterferon, ribavirin, and sofosbuvir.

The rate of adverse events was significantly different among the studied groups with lowest rate in group 4. The most common reported adverse events in group 1 were flu like illness and anemia. Flu like symptoms are related to use of interferon [29], whereas anemia is known to be frequent in ribavirin-inclusive combinations [30]. Ribavirin-induced anemia is a well described phenomenon [31].

In group 2, anemia, hyperbilirubinemia and fatigue were the most frequent side effects, while in group 3, hyperbilirubinemia and fatigue were the main adverse events. In group 4, only two adverse events have been reported; hyperbilirubinemia and anemia.

Hyper bilirubinemia during treatment with SMV/SOF and DCV/SOF was recorded also by Babatin et al [28].Hyperbilirubinemia during SOF/ SMV therapy was also documented Yosry et al [6]. These changes are transient and normalized during the course of treatment despite the continuation of DAAs.

According the practice guidelines during the study period sofosbuvir was not allowed for patients with severe renal impairment or with end-stage renal disease and hence patients with severe renal impairment were excluded from this study because 80% of sofosbuvir is excreted through the kidney [32].

Also, patients with active hepatocellular carcinoma (HCC) or recently treated HCC has been ruled out. Rates of HCC recurrence after

DAAs were extremely variable in different studies **[33]**. The possibility that treatment with DAAs may favor tumor growth and spread in individual patients with active HCC foci is suggested by some observations **[6]**.

In this study the high overall SVR was confirming the efficacy of DAA-based regimens, similar to COSMOS **[34]**, ALLY-3 **[27]**, and even to European **[35]**and North American [36] real-life studies. Oral therapy may be a reasonable option for patients with compensated cirrhosis as well as patients who failed to respond to previous therapy.

The current study had its own limitations. First, inclusion of IFN-based regimens, those are currently obsolete for HCV management. Second, the lack of evaluation of the newer generations of DAAs e.g. velpatasvir that seems effective in both compensated and decompensated HCV related cirrhosis. These because the period covered by the study was in the early era of HCV management by DAAs. The probability of selection bias among patients' enrolment to each therapeutic arm.

In conclusion, oral HCV SOF-based treatments are associated with high rates of SVR and a good tolerance for patients in real life.The combination of sofosbuvir with daclatasvir was associated with high cure rates in naïve, cirrhotic and treatment experienced patients. Regarding the safety of SOF-based oral therapy, in general, it was safe and well tolerated.

DECLARATIONS
Ethics approval and consent to participate: Approved

Competing interests: None declared

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List of Abbreviations

HCV: Hepatitis C virus
CDC: Center for Disease Control
SOF: Sofosbuvir
PEG-IFN: Pegylated interferon
 DAC: Daclatasvir
SIM: Simeprevir
SVR:Sustained virological response
DAAs:Direct-acting antivirals
RBV:Ribavirin
CTP: Child Turcotte Pugh
ALT:Alanine aminotransferase
AST:Aspartate aminotransferase
AFP:Alpha fetoprotein
HCV PCR:Hepatitis C virus polymerase chain reaction
CBC:Complete blood count
INR:International normalized ratio
ESLD:End-stage liver disease
LT:Liver transplantation
HCC:Hepatocellular carcinoma
SPSS:Statistical Package for Social Sciences
EOT:End of treatment

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