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Original article

Sofosbuvir plus Ribavirin for Treatment-Naïve Chronic HCV Genotype 4 Patients: Real-life Experience

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Abstract:
New regimens involving direct-acting antiviral agents have recently been approved for the treatment of genotype 4 HCV. Our aim was to assess the efficacy and safety of 12 or 24 weeks of Sofosbuvir plus ribavirin in treating patients with chronic genotype 4 hepatitis C virus infection. This is an open-label observational study that describes the effect of 12 week or 24 weeks of daily oral Sofosbuvir 400 mg and ribavirin 1000-12000 mg with dose adjustment if indicated. It includes the first 813 patients that fulfil the inclusion and exclusion criteria and treated in Egyptian Liver Research Institute and Hospital (ELRIAH), Mansoura, Egypt. By week 4 of therapy 100% of patients had undetectable HCV RNA and all maintained virological suppression during therapy. SVR12 was achieved by 113 (77.4%) of the patients receiving 12 weeks of treatment, and by 622 (93.3%) of the patients receiving 24 weeks of treatment. SVR12 rates were significantly higher in patients with no cirrhosis, (86.3% for 12 weeks and 95.5% for 24 weeks) than in patients with cirrhosis (56.8% for 12 weeks and 87.0% for 24 weeks). The most common adverse events in both groups were anemia, headache, epigastric pain, insomnia, and heart burn. No serious adverse events were reported in the studied groups. No adverse events resulted in interruption of RBV. No patients had adverse events leading to dose modification or discontinuation of sofosbuvir. Treatment with Sofosbuvir and ribavirin for 12 or 24 weeks was effective and well tolerated in patients with genotype 4 HCV.

Abbreviations: *BMI*; Body Mass Index. *DAA*; Direct Acting Antivirals. *HCV*; Hepatitis C Virus. *kPa*; Kilo Pascals. *LLOQ*; Lower Limit of Quantification. *PegIFNα*; Pegylated Interferon Alpha. *RBV*; Ribavirin. *RNA*; Ribonucleic acid. *SD*; Standard Deviation. *SOF*; Sofosbuvir. *SPSS*; Statistical Package for Social Sciences. *SVR*; Sustained Virologic Response. *SVR12*; Sustained Virologic Response after 12 weeks. *ULN*; Upper Limit of Normal.

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1. Introduction

Chronic hepatitis C virus (HCV) infection affects an estimated 170 million people worldwide [1] with the highest prevalence in Egypt, where over 90% of the infections have been reported to be HCV genotype 4 [2]. Patients with HCV infection are at risk for developing end-stage liver disease with a variety of complications including hepatocellular carcinoma and decompensated cirrhosis with elevated risk of liver related mortality [3]. Until recently, therapy for genotype 4 HCV has been pegylated interferon (PegIFNα) with ribavirin (RBV) for 24 to 48 weeks, depending on virologic response. Treatment-naïve patients receiving this regimen have sustained virologic response (SVR) rates of 43% to 70% [4]. As a result of difficulty in administration and poor tolerability associated with PegIFNα and RBV, treatment uptake has been low, and most patients with HCV in Egypt are untreated [5]. New regimens involving direct-acting antiviral agents (DAAs) have recently been approved for the treatment of genotype 4 HCV. These regimens appear to offer improved rates of SVR in treatment-naïve and previously treated patients with genotype 4 HCV [6]. Sofosbuvir (SOF) is a nucleotide analogue inhibitor of HCV NS5B polymerase with activity against all HCV genotypes [7]. It has a favorable safety profile and most adverse reaction have been attributed to the concurrent use of PegIFNα or RBV [8]. The interferon-free regimen for genotype 4 HCV infection could have a major impact on the burden of HCV, particularly in Egypt. Evaluating the effectiveness of SOF plus RBV regimen in real-world setting is essential to provide practical information to better inform HCV treatment decisions. Our aim was to assess the efficacy and safety of 12 or 24 weeks of SOF plus RBV in treating patients with chronic genotype 4 HCV infection at Egyptian Liver Research Institute and Hospital (ELRIAH), Mansoura, Egypt.

2. Patients and Methods

2.1. *Study design*

This is an open-label observational study that describes the effect of 12 week or 24 week of daily oral SOF 400 mg and RBV 1000-12000 mg with dose adjustment if indicated. It includes 813 patients that fulfil the inclusion and exclusion criteria and treated in Egyptian Liver Research Institute and Hospital (ELRIAH), Mansoura, Egypt, in the period between August 2014 and August 2015. At that time, there were no guidelines that regulate the period of treatment (12/24 weeks), so decision on period of treatment were done according to clinical decision only.

2.2. *Patients*

Patients were required to be at least 18 years of age with body mass index ≥18 kg/m^2 and had chronic genotype 4 HCV infection with a serum HCV RNA level ≥10^4 log IU/ml. Patients could have compensated cirrhosis. Cirrhosis was defined by (1) liver biopsy indicating liver fibrosis stage 4 (Metavir) prior to treatment initiation and (2) liver biopsy indicating stage 3 fibrosis prior to treatment initiation in combination with any of the following clinical parameters: platelets <100 x 10^3/L, esophageal varices on endoscopy, cirrhosis and/or portal hypertension and/or ascites by imaging methods. If a liver biopsy was not available, cirrhosis was defined by evidence for two of the following variables, platelets <100 x 10^3/L, esophageal varices on endoscopy, cirrhosis and/or portal hypertension and/or ascites by imaging methods. Cirrhosis was also determined by FibroScan level >16.2 kPa [9]. The following patients were excluded from the study: patients with treatment experiences for HCV, decompensated cirrhosis, HIV or hepatitis B virus infection, chronic liver disease of non HCV etiology, direct bilirubin ≥1.5 times the upper limit of normal (ULN), alanine and aspartate aminotransferase >10 times ULN, hemoglobin <12 g/dl for men and <11 g/dl for women, platelets <50,000/μl, hemoglobin A1c >10%, and creatinine clearance <60 ml/min.

2.3. *Efficacy assessment*

Serum HCV RNA was determined using the Roche COBAS TaqMan HCV Test v2.0 (Roche Molecular Systems, Pleasanton, California, USA; lower limit of quantitation (LLOQ) of 25 IU/ml) at baseline, at weeks 1, 2, 4, 6, 8, 10, 12 of treatment for all patients plus at weeks 16, 20, 24 for patients receiving 24 weeks therapy and post-treatment weeks 4 and 12. Primary efficacy endpoint was SVR12 defined as HCV RNA below the LLOQ or undetectable at least 12 weeks after treatment was discontinued.

2.4. *Safety assessments*

Safety evaluation was done by collecting data during treatment up to 30 days after the last dose by assessment of physical examination, vital sign measurements, ECG recordings, clinical laboratory tests, and documentation of adverse effects.

2.5. *Ethics*

The study was conducted in accordance to the Declaration of Helsinki and International Conference on Harmonization guidelines. Our study did not require approval from the ethics committee since it was performed as an observational study in the context of normal clinical routine. However, all patients provided informed consent for the use of their data for research purposes. Blood samples were obtained as part of standard patient care؛ samples and data were anonymous.

2.6. *Statistical assessments*

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 21.0 for Windows (IBM Corp., USA). P value <0.05 was considered statistically significant. The quantitative data was described with mean and standard deviation (SD), and the qualitative data was described by frequency and percent. Quantitative variables were compared with the student t-test. The comparison between qualitative independent variables was performed by the Chi-square test.

3. Results

3.1. *Study population*

The study was conducted in the Egyptian Liver Research Institute and Hospital (ELRIAH), Mansoura, Egypt, From August 2014 through August 2015, where 813 patients were included in the study and completed treatment with SOF plus RBV for 12 weeks (n = 146) or 24 weeks (n = 667). The mean age of enrolled patients was 51.5±10.7 years, 63.6% were men, and 60.4% had a body mass index ≥30 kg/m^2. Mean HCV RNA levels were 5.43 log10 IU/ml and 221 (27.2%) patients had cirrhosis. Cirrhosis was diagnosed clinically in 99 (12.2%) patients and by FibroScan testing in 122 (15%) patients, table (1).

3.2. *Efficacy*

By week 4 of therapy 100% of patients had undetectable HCV RNA and all maintained virological suppression during therapy. SVR12 was achieved by 113 (77.4%) of the patients receiving 12 weeks of treatment, and was higher 622 (93.3%) in patients receiving 24 weeks of treatment, table (2). SVR12 rates were significantly higher in patients with no cirrhosis, (86.3% 12 weeks, 95.5% 24 weeks) than in patients with cirrhosis (56.8% 12 weeks, 87.0% 24 weeks). SVR12 was lower in patient with FibroScan >10.2 kPa in patient receiving 12 weeks treatment. HCV RNA viral load and gender did not appear to have an effect on SVR12 rate in the studied patients, table (3).

3.3. *Safety*

The most common adverse events in both groups were anemia, headache, epigastric pain, insomnia, and heart burn, table (4). Although most adverse effects were more common in patients treated for 24 weeks, this does not appear to be explained simply by longer duration, since the differences between the groups were recorded during the first 12 weeks of treatment. No serious adverse events were reported in the studied groups. No adverse events resulted in interruption of RBV. No patients had adverse events leading to dose modification or discontinuation of SOF. Dose modification of RBV was needed in 10 (6.8%) of patients receiving 12 weeks of treatment and in 135 (20.2%) of those receiving 24 weeks.

Table (1) Patient demographics and baseline characteristics.

Characteristic	12 weeks n = 146	24 weeks n = 667	P-value
Mean (SD) age, yr	49.5 (10.9)	51.9 (10.7)	0.017
Sex, male, n (%)	100/146 (68.5)	417/667 (62.5)	0.174
BMI <30 kg/m^2, n (%)	26/73 (35.6)	73/177 (41.2)	0.408
Mean (SD) HCV RNA, log10 IU/ml	5.4 (0.96)	5.5 (0.93)	0.306
Cirrhosis, n (%)	--	--	--
Present	44/146 (30.1)	177/667 (26.5)	0.376
Method of cirrhosis detection, n (%)	--	--	--
• **Clinically**	20 (45.5)	79 (44.6)	--
• **FibroScan (significant fibrosis >16.2 kPa)$^{\#}$**	24 (54.5)	98 (55.4)	--
Platelets <100 x 10^3/L, n (%)	30/134 (22.4)	96/609 (15.8)	0.064
Albumin <3.5 g/dl, n (%)	13/128 (10.2)	71/546 (13.0)	0.380

BMI: body mass index; HCV: hepatitis C virus. # According to Shiha et al., 2014 [9]

Table (2) Virological response after 3 months of treatment (SVR12)

	12 weeks n = 146	24 weeks n = 667	P-value
All patients	113/146 (77.4)	622/667 (93.3)	<0.001
No cirrhosis	88/102 (86.3)	468/490 (95.5)	<0.001
Cirrhosis	25/44 (56.8)	154/177 (87.0)	<0.001

SVR12, sustained virological response. Data is presented as no./total no. (%)

Table (3) Virological response after 3 months of treatment (SVR12) by patient groups

Treatment Group	12 weeks n = 146	24 weeks n = 667	P-value
No cirrhosis	88/102 (86.3)	468/490 (95.5)	<0.001
Cirrhosis	25/44 (56.8)	154/177 (87.0)	<0.001
P value	<0.001	<0.001	--
Male	74/100 (74.0)	385/417 (92.3)	<0.001
Female	39/46 (84.8)	237/250 (94.8)	0.013
P value	0.148	0.218	--
HCV RNA, <600,000 IU/ml	59/72 (81.9)	275/293 (93.9)	0.001
HCV RNA, >=600,000 IU/ml	37/49 (75.5)	195/210 (92.9)	<0.001
P value	0.391	0.655	--
FibroScan <10.2 kPa #	25/29 (86.2)	88/93 (94.6)	0.130
FibroScan >=10.2 kPa #	20/33 (60.6)	144/159 (90.6)	<0.001
P value	0.024	0.250	--

SVR12, sustained virological response. Data is presented as no./total no. (%)
 # Cut off point discriminating F0-2 and F3-4 according to Shiha et al., 2014 [9]

Table (4) Treatment-emergent adverse events

--	12 weeks n = 146	24 weeks n = 667	P-value
No. (%) of patients with any adverse event	11 (7.5)	160 (24.0)	<0.001
No. of patients with a serious adverse event	0	0	NA
Adverse event leading to discontinuation, No.	0	0	NA
No. (%) of patients with adverse events leading to RBV dose modification	10 (6.8)	135 (20.2)	<0.001
Deaths, n	0	0	NA
Adverse events, No. (%)	--	--	--
- ***Anemia***	11 (7.5)	133 (19.9)	--
- ***Headache***	5 (3.4)	90 (13.2)	--
- ***Epigastric pain***	4 (2.7)	28 (4.2)	--
- ***Insomnia***	0 (0.0)	25 (3.7)	--
- ***Heart burn***	0 (0.0)	23 (3.4)	--
- ***Constipation***	0 (0.0)	14 (2.1)	--
- ***Fatigue***	0 (0.0)	12 (1.8)	--
- ***Hypotension***	0 (0.0)	10 (1.5)	--

4. Discussion

Prior to the introduction of DAAs, combined PegIFNα and RBV treatment for 48 or 24 weeks was the standard of care for patients with genotype 4 [10]. Given the scale of the HCV epidemic in Egypt, a treatment regimen that is simple and of short duration is critical for treatment uptake to be widespread and successful. In this open-label study involving previously untreated patients with genotype 4 HCV infection, we investigated the efficacy and tolerability of SOF and RBV treatment administered for 12 or 24 weeks. The results of this study suggest an interferon-free regimen of SOF and RBV for either 12 or 24 weeks is successful in treating treatment-naïve patients with genotype 4 HCV. The rate of SVR12 was significantly higher in the group receiving 24 (93.3%) vs. 12 (77.4%) weeks of therapy. The presence of cirrhosis was associated with lower rates of SVR12 in both the 12 and 24 week groups. Undergoing 24 vs. 12 weeks of treatment appears to have some benefit, especially for patients who have cirrhosis. The results in this study are consistent with other studies evaluating treatment with SOF plus RBV for 12 or 24 weeks in Egyptian patients with genotype 4 HCV infection [11,12]. In Ruane et al. study on patients of Egyptian origin [11], SVR12 rates were 68% (21/31) following 12 weeks of treatment and 93% (27/29) following 24 weeks of treatment. Although only a small number of patients had cirrhosis, 43% (3/7) receiving 12 weeks of treatment and 100% (7/7) receiving 24 weeks achieved SVR12. In Doss et al. study [12] in Egyptian patients, SVR12 rates were 90% (46/51) with 24 weeks and 77% (40/52) with 12

weeks of SOF and RBV therapy. Patients with cirrhosis at baseline had lower rates of SVR12 (63% for 12 weeks, 78% for 24 weeks) than those without cirrhosis (80% for 12 weeks, 93% for 24 weeks). Few studies have reported real-world, clinical practice outcomes for SOF and RBV for treatment of other genotypes (other than type 4) HCV infection. TRIO Health study [13] evaluated the efficacy of SOF/RBV for 12 weeks in a real-world US population of genotype 2 infected patients. SVR rates were 71% in patients with liver cirrhosis and 89% in patients without cirrhosis. Another observational study investigated the effectiveness of SOF/RBV in genotype 2 infected US veterans [14], and reported 81.6% SVR rate in treatment-naïve non cirrhotic patients., while SVR12 rates were 58.2% in patients with advanced liver disease. In HCV TARGET observational study for genotype 2 HCV infection, overall SVR12 was 88.2%. In patients without cirrhosis it was 91.0% and 92.9% for 12 or 16 weeks of therapy respectively. In patients with cirrhosis it was 79.0% and 83% [15]. Mangia et al. [16] investigated SVR rates attained in an Italian real life HCV cohort with genotype 2. SVR rates for cirrhotics was 94.51%, and 94.94% after 16 or 20 weeks respectively. Shah et al. [17] evaluated the efficacy and safety of SOF plus RBV therapy among treatment-naïve patients with chronic genotype 1 or 3 HCV infection in India. SVR12 was reported in 90% and 96% of patients following 16 and 24 weeks of treatment, respectively, Treatment with SOF plus RBV was well tolerated in all patient subgroups, including those with advanced liver disease. The most common treatment-related adverse events were anemia, headache, epigastric pain and insomnia; and these adverse events are consistent with adverse events known to be cause by RBV. The overall safety profile of SOF plus RBV therapy was similar to that of prior studies with regard to the types of adverse events [11,12].

5. Conclusion

The results from this study indicate that treatment with all-oral regimen of Sofosbuvir and ribavirin for 12 or 24 weeks was effective and well tolerated in patients with genotype 4 HCV. Undergoing 24 vs. 12 weeks of treatment appears to have some benefit, especially for patients who have cirrhosis. Egypt, which is experiencing an epidemic of HCV, may benefit from the availability of an all-oral therapy. However, as this clinical practice study has a non-randomized, observational design, differences between treatment groups should be interpreted cautiously.

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