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ORIGINAL ARTICLE

Impact of Two Sofosbuvir-Containing Regimens on the Haematological and Biochemical Profiles of Egyptian Patients with Hepatitis C-related Compensated Cirrhosis

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ABSTRACT

AIM: This study aimed to evaluate the efficacy and safety of sofosbuvir (SOF)/ribavirin (RBV) and SOF/daclatasvir (DAC)/RBV in Egyptian patients with hepatitis C virus (HCV)-related cirrhosis and to demonstrate the effects of these treatments on their haematological and biochemical profiles.

PATIENTS AND METHODS: A prospective study was performed on 200 patients with HCV-related cirrhosis. Group 1 received SOF and RBV for 24 weeks, and Group 2 received SOF, DAC and RBV for 12 weeks.

RESULTS: A sustained virological response (SVR) was achieved in 75 (75%) and 96 (96%) patients in Groups 1 and 2, respectively. The mean haemoglobin (Hb) level and platelet count decreased significantly at the end of treatment in both groups, and the percent decrease was significantly higher in Group 1 than in Group 2. The mean albumin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels decreased significantly at the end of treatment in both groups. There was a significant increase in the mean total bilirubin level in both groups at the end of treatment. The percent increase in the mean indirect bilirubin level was significantly higher in Group 2 than in Group 1. There was improvement in the Fibrosis-4 (FIB-4) score at the end of treatment in both groups. This improvement was maintained to SVR 12 in both groups.

CONCLUSION: Patients with cirrhosis who received SOF, DAC and RBV for 12 weeks had a significantly higher SVR12 rate than those who received SOF and RBV for 24 weeks. In patients who achieved SVR, there was improvement in liver function parameters and the FIB4 score at the time of SVR12 in compared to baseline values.

Key words: Liver cirrhosis; Sofosbuvir; Daclatasvir; Ribavirin; Haematological; Biochemical profile

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INTRODUCTION

Hepatitis C is a global health problem, and the World Health Organization (WHO) has not previously formulated estimates of the number of persons living with hepatitis C virus (HCV). Mohd Hanafiah *et*

al[1] found that globally, the prevalence and number of people with anti-HCV were 2.8% and >185 million, respectively. Gower *et al*[2] demonstrated that 80 million persons had HCV infection.

The primary aim of antiviral therapy for HCV is to improve clinical outcomes through eradication of the infection. Sustained virological response (SVR) appears to be a reasonable marker for virological eradication because this parameter is correlated to the loss of detectable intrahepatic HCV RNA[3] and is durable, as < 1% of individuals who achieved an SVR subsequently tested positive for serum HCV RNA[4].

Treatment of chronic hepatitis C with pegylated interferon-alpha (PEG-α) and ribavirin (RBV) (PR) is limited by an unfavourable side effect profile and the results of sustained viral suppression in < 50% of those infected with HCV genotype 1 and approximately 65%, 75% and 80% with genotypes 4, 3 and 2, respectively[5].

A better understanding of the HCV life cycle and viral enzymes that are potential antiviral targets[6] has led to the establishment of a number of new direct-acting antiviral agents (DAAs) directed against viral proteins[7].

Treatment with these new DAAs has resulted in marked improvement in SVR among HCV-infected patients from approximately 5% with interferon monotherapy in the early 1990s to > 95% today with DAA combinations[8].

Aim of the work

To assess the efficacy and safety of sofosbuvir (SOF)/RBV and SOF/daclatasvir (DAC)/-RBV in Egyptian HCV patients with compensated cirrhosis and to determine the changes in the haematological and biochemical profiles of these patients at the end of therapy and at the time of SVR.

PATIENTS AND METHODS

Patient population

A prospective study was performed on two hundred patients with HCV-related cirrhosis (treatment-naive). The patients were recruited from the National Viral Hepatitis Treatment Center and started treatment for HCV based on the national guidelines. The diagnosis of liver cirrhosis was confirmed based on the clinical criteria for liver cirrhosis, ultrasound findings, low serum albumin levels, impaired prothrombin time, Fibroscan ≥ 14.5 kPa and or, liver biopsy findings (Metavir = F4), and/or the presence of oesophageal or gastric varices on upper endoscopy.

Exclusion criteria

Patients with a combination of HCV and hepatitis B virus (HBV), hepatocellular carcinoma (HCC), and a current or past history of ascites or hepatic encephalopathy were excluded.

Treatment regimen

Two hundred treatment-naive patients with compensated HCV-related liver cirrhosis were included. These patients had started HCV treatment according to the national guidelines during two periods (from January 2015 to March 2015 for Group 1) and (from February 2016 to March 2016 for Group 2). Group 1 received SOF (400 mg once daily) and RBV (1000 mg/day if body weight < 75 kg or 1200 mg/day if body weight ≥ 75 kg) for 24 weeks, and Group 2 received SOF (400 mg once daily), DAC (60 mg once daily) and RBV (at initial dose of 600 mg/day, which was increased as tolerated) for 12 weeks.

Methods

Clinical and laboratory evaluations were performed. Investigations including liver function tests (LFTs), a complete blood count (CBC), quantitative HCV RNA levels, abdominal ultrasound and **calculation of the Fibrosis-4 (FIB4) score**[9] were performed for all patients at baseline.

During treatment, clinical evaluation and laboratory investigations (CBC and LFTs) were performed in Group 1 patients every month for 6 months and in Group 2 patients every month for 3 months.

HCV RNA levels were measured with quantitative polymerase chain reaction (PCR) at end of treatment. **Abdominal ultrasound** and **calculation of the FIB4** score were performed at the end of treatment**.**

Renal function (urea and creatinine levels) was assessed at baseline, at the end of treatment and at the time of SVR.

Patients who achieved end treatment response (ETR) underwent follow-up evaluation 3 months after ETR including a full clinical evaluation, laboratory investigation (CBC and LFTs), abdominal ultrasound, measurement of HCV RNA levels with quantitative PCR and calculation of the FIB4 score.

Serum HCV RNA levels were measured using a quantitative PCR assay (Cobas Amplicor, HCV Roche, Branchburg, NJ, USA, v 2.0, detection limit 15 IU/ml).

The virological response was assessed according to the definition of different response patterns reported by Franciscus, 2015[10]. ETR was defined as HCV RNA < 15 IU/mL at the end of the treatment. SVR 12 weeks after the end of treatment (SVR12) was defined as HCV RNA < 15 IU/mL at 12 weeks following the completion of treatment. Relapse was defined as the reappearance of HCV RNA at 12 weeks post-treatment in patients who achieved ETR.

Ethical consideration

The study was approved by the Ethics Committee of the Faculty of Medicine. Written informed consent was obtained from all participants.

Statistical analysis

Statistical Package for Social Science Version 19.0, SPSS Inc., Chicago, Ill., USA was used. Data are presented as numbers, percentages, means and standard deviations. The chi-square test and Fisher's exact test were used to compare qualitative variables. The Mann-Whitney test was used to compare quantitative variables between both groups. Data were non-parametric, and the Wilcoxon signed rank test was performed to compare the quantitative variables at baseline and at the end of treatment. *P* values were considered statistically significant if < 0.05. The percent change was calculated as 100 × (value of the variable at the end of the treatment - value of the variable at baseline) / value of the variable at baseline.

RESULTS

Both groups of patients HCV-related compensated liver cirrhosis were age- and sex-matched. The mean ages were 55.64 ± 7.73 and 57.40 ± 7.06 in groups 1 and 2, respectively (p = 0.197). Fifty percent of the patients were men in both groups (p value = 1.000). The mean body mass index (BMI) was higher in Group 1 (28.70 ± 3.88 kg/m^2) than in Group 2 (26.95 ± 4.21 kg/m^2) (p = 0.002).

Baseline laboratory data of the studied groups

Patients in Group 1 had significantly higher indirect bilirubin levels that were still within the normal range and significantly higher international normalized ratio (INR) but significantly lower alanine aminotransferase (ALT) and albumin levels than those in Group 2 (p < 0.05). Group 2 had higher median HCV RNA levels than Group

1 (p = 0.006). We found no significant difference between the two groups regarding the mean alpha-fetoprotein (AFP) level.

Regarding baseline CBC indices, the mean platelet (PLT) count was significantly lower in Group 1 than in Group 2. However, there was no significant difference between the groups regarding the mean white blood cells (WBCs) count or haemoglobin (Hb) level (Table 1).

Virological response

ETR occurred in 98 patients in Group 1 (98%) and 100 patients in Group 2 (100%). SVR three months after the end of treatment (SVR12) occurred in 75 (75%) and 96 (96%) patients in Groups 1 and 2, respectively. Relapse occurred in 23 patients (23%) in Group 1 and 4 patients (4%) in Group 2. Group 2 had a significantly higher SVR12 rate and a significantly lower relapse than Group 1 (p < 0.001) (Figure 1).

Table 1 Baseline laboratory data of the studied groups.

Variables (normal range)	Group 1 (n = 100)	Group 2 (n = 100)	P-value[3]
	Mean ± SD	Mean ± SD	
ALT (0-41 U/L)	58.30 ± 21.92	64.05 ± 32.99	0.016*
AST (0-38 U/L)	69.25 ± 22.97	62.81 ± 28.11	0.742
Bilirubin (0-1 mg/dl)	1.10 ± 0.43	0.98 ± 0.37	0.055
Indirect bilirubin (0-0.75 mg/dl)	0.67 ± 0.23	0.52 ± 0.20	< 0.001*
Albumin (3.5-5 g/dl)	3.42 ± 0.38	3.66 ± 0.48	< 0.001*
INR (0.9-1.22)	1.26 ± 0.13	1.20 ± 0.15	0.002*
Creatinine (0.5-1.2 mg/dl)	0.84 ± 0.16	0.87 ± 0.13	0.102
TLC (4-11 × 10^3/mm³)	5.07 ± 1.33	5.47 ± 1.55	0.093
ANC (2-7 × 10^3/mm³)	2.52 ± 0.70	2.66 ± 0.75	0.159
Hb (12-17 g/dl)	12.88 ± 1.09	12.98 ± 1.35	0.685
PLT (150-450 × 10^3/mm³)	128.75 ± 31.57	147.69 ± 37.67	< 0.001*
AFP (0-10.9 ng/ml)	16.61 ± 19.14	13.92 ± 14.37	0.287
HCV RNA ¶ (< 15 IU/ml)	273,500 (1,240-10,000,000)	435,500 (271-38,728,000)	0.006*

Data are expressed as the mean (SD). ¶ Data are expressed as the median (range). P was considered significant if < 0.05. AFP: alpha-fetoprotein; ALT, alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; Hb: haemoglobin; HCV RNA: hepatitis C virus ribonucleic acid; INR: international normalized ratio; PLT: platelet; TLC: total leucocyte count. Group 1: patients received sofosbuvir and ribavirin for six months; Group 2: patients received sofosbuvir, daclatasvir and ribavirin for three months.

Changes in CBC parameters and creatinine levels in Group 1 patients during the study period are shown in Table 2

The mean total leukocyte count (TLC) and absolute neutrophil count (ANC) showed significant decreases during the treatment period. The mean Hb level showed a significant decrease during the treatment period and during the first three months of the follow-up period. The mean PLT count showed a non-significant change during the first 2 months of treatment. After that, there was a significant decrease in the mean PLT count until 3 months after the end of treatment.

There was no significant change in the mean serum creatinine level at the end of therapy compared to baseline level.

Changes in LFTs in Group 1 patients during the study period are shown in Table 3

There was a significant decrease in the mean AST and ALT levels during the course of treatment, and this significant decrease compared to the mean baseline levels was maintained until SVR.

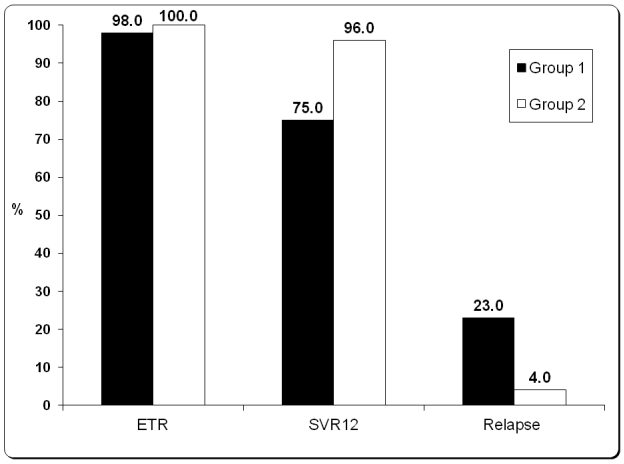

Figure 1 Virological Response with Different Regimens in the Present Study.

Table 2 Changes in CBC parameters and creatinine levels in Group 1 patients during the study period.

Time of follow-up	TLC (4-11 × 10^3/mm³)	ANC (2-7 × 10^3/mm³)	Haemoglobin (12-17 g/dl)	Platelets (150-450 × 10^3/mm³)	Creatinine (0.5-1.2 mg/dl)
Baseline	5.07 ± 1.33	2.52 ± 0.70	12.88 ± 1.09	128.75 ± 31.57	0.84 ± 0.16
1st month	4.86 ± 1.24	2.45 ± 0.66	11.82 ± 1.21	128.00 ± 31.81	--
2nd month	4.63 ± 1.20	2.30 ± 0.63	11.38 ± 1.16	128.69 ± 32.81	--
3rd month	4.48 ± 1.21	2.24 ± 0.61	11.35 ± 1.09	126.19 ± 31.56	--
4th month	4.36 ± 1.27	2.19 ± 0.67	11.26 ± 1.11	124.42 ± 31.49	--
5th month	4.21 ± 1.23	2.09 ± 0.65	11.23 ± 1.06	124.45 ± 31.06	--
End of therapy	4.09 ± 1.12	2.03 ± 0.55	11.23 ± 1.05	124.65 ± 31.38	0.86 ± 0.10
3 months after therapy	4.91 ± 1.01	2.39 ± 0.49	12.66 ± 0.87	127.06 ± 30.18	0.83 ± 0.08
P-value1	0.001*	0.053	< 0.001*	0.183	--
P-value2	< 0.001*	< 0.001*	< 0.001*	0.876	--
P-value3	< 0.001*	< 0.001*	< 0.001*	0.003*	--
P-value4	< 0.001*	< 0.001*	< 0.001*	< 0.001*	--
P-value5	< 0.001*	< 0.001*	< 0.001*	< 0.001*	--
P-value6	< 0.001*	< 0.001*	< 0.001*	< 0.001*	0.199
P-value7	0.008*	0.009*	< 0.001*	< 0.001*	0.651

Data are expressed as the mean (SD). P was considered significant if < 0.05. TLC: total leucocyte count; ANC, absolute neutrophil count; CBC: complete blood count. P-value1: compared baseline with 1st month; P-value2: compared baseline with 2nd month; P-value3: compared baseline with 3rd month; P-value4: compared baseline with 4th month; P-value5: compared baseline with 5th month; P-value6: compared baseline with the end of therapy; P-value7: compared baseline with 3 months after therapy.

There was a significant increase in the mean total and indirect bilirubin levels during treatment. The total bilirubin level decreased at the time of SVR.

After starting antiviral treatment (SOF/RBV), there was a significant decrease in the mean albumin level and a significant increase in the mean INR compared to baseline levels. However, at the end of treatment, there was a non-significant change in the mean INR, but there was still a significant decrease in the mean albumin level compared to the baseline level ($p < 0.05$). At the time of SVR, all of these synthetic liver function parameters were significantly improved.

Changes in CBC parameters and creatinine levels in Group 2 patients during the study period are shown in Table 4

The mean TLC, Hb level and ANC were significantly decreased during therapy compared to baseline values. However, at the time of SVR, the mean TLC, ANC, and Hb level increased further but still remained decreased compared with baseline values.

There was a significant mild decrease in the mean PLT count during treatment and at the end of treatment. However, at the time of SVR, there was no significant increase in the mean PLT count. There was no significant change in the mean serum creatinine level at the end of treatment compared to the baseline mean level ($p > 0.05$).

Changes in LFTs in Group 2 patients during the study period are shown in Table 5.

There was significant improvement in the mean ALT and AST levels during treatment and at the time of SVR compared to baseline levels ($p < 0.05$).

The mean total bilirubin and indirect bilirubin levels were significantly increased during therapy. At 3 months of follow-up (SVR), there was a significant decrease in the mean total bilirubin and indirect bilirubin levels, but these levels were still higher than baseline levels.

During the treatment period, there was a significant decrease in the mean albumin level and a significant increase in the mean INR. At 3 months after the end of treatment (SVR), there was no significant increase in the mean albumin level and significant improvement (decrease) in the mean INR compared to baseline values.

Changes in the haematological and biochemical parameters and FIB4 scores at ETR compared to baseline in both study groups are shown in Table 6.

The mean Hb level significantly decreased at the end of treatment in both groups ($p < 0.001$ for each). The percent decrease in the mean Hb level was significantly higher in Group 1 than in Group 2 ($p = 0.006$).

Table 3 Changes in liver function tests in Group 1 patients during the study period.

Time of follow-up	ALT (0-41 U/L)	AST (0-38 U/L)	Bilirubin (0-1 mg/dl)	Indirect bilirubin (0-0.75 mg/dl)	Albumin (3.5-5 g/dl)	INR (0.9-1.22)
Baseline	58.30 ± 21.92	69.25 ± 22.97	1.10 ± 0.43	0.67 ± 0.23	3.42 ± 0.38	1.26 ± 0.13
1st month	41.74 ± 13.96	46.58 ± 13.83	1.51 ± 0.55	0.97 ± 0.36	3.38 ± 0.35	1.27 ± 0.13
2nd month	35.83 ± 11.09	39.10 ± 11.39	1.53 ± 0.51	0.99 ± 0.32	3.34 ± 0.36	1.28 ± 0.13
3rd month	34.15 ± 10.44	37.08 ± 10.35	1.43 ± 0.46	0.90 ± 0.28	3.35 ± 0.36	1.27 ± 0.13
4th month	31.70 ± 9.77	36.46 ± 9.48	1.44 ± 0.42	0.90 ± 0.24	3.33 ± 0.34	1.28 ± 0.13
5th month	30.26 ± 9.53	35.21 ± 8.88	1.40 ± 0.44	0.90 ± 0.25	3.35 ± 0.35	1.28 ± 0.13
End of therapy	30.09 ± 8.75	34.61 ± 8.38	1.37 ± 0.41	0.89 ± 0.25	3.37 ± 0.35	1.26 ± 0.13
3 months after therapy	31.94 ± 13.34	35.52 ± 11.66	1.10 ± 0.34	0.68 ± 0.18	3.47 ± 0.35	1.24 ± 0.13
P-value1	< 0.001*	< 0.001*	< 0.001*	< 0.001*	0.001*	0.001*
P-value2	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	0.002*
P-value3	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	0.005*
P-value4	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	0.002*
P-value5	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	0.003*
P-value6	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	0.401
P-value7	< 0.001*	< 0.001*	0.759	0.593	< 0.001*	< 0.001*

Data are expressed in form of mean (SD). P value was significant if < 0.05. ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio. P-value1: compared baseline with 1st month; P-value2: compared baseline with 2nd month; P-value3: compared baseline with 3rd month; P-value4: compared baseline with 4th month; P-value5: compared baseline with 5th month; P-value6: compared baseline with the end of therapy; P-value7: compared baseline with 3 months after therapy.

Table 4 Changes in CBC parameters and creatinine levels in Group 2 patients during the study period.

Time of follow-up	TLC (4-11 × 10^3/mm^3)	ANC (2-7 × 10^3/mm^3)	Haemoglobin (12-17 g/dl)	Platelets (150-450 × 10^3/mm^3)	Creatinine (0.5-1.2 mg/dl)
Baseline	5.47 ± 1.55	2.66 ± 0.75	12.98 ± 1.35	147.69 ± 37.67	0.87 ± 0.13
1st month	5.25 ± 1.41	2.55 ± 0.69	12.26 ± 1.36	145.40 ± 36.56	--
2nd month	4.96 ± 1.36	2.41 ± 0.67	11.81 ± 1.39	146.82 ± 37.63	--
End of therapy	4.74 ± 1.20	2.28 ± 0.57	11.66 ± 1.28	145.30 ± 36.46	0.85 ± 0.09
3 months after therapy	5.29 ± 1.14	2.55 ± 0.63	12.60 ± 1.21	149.21 ± 35.75	0.83 ± 0.07
P-value1	0.001*	0.007*	< 0.001*	0.002*	--
P-value2	< 0.001*	< 0.001*	< 0.001*	0.361	--
P-value3	< 0.001*	< 0.001*	< 0.001*	0.005*	0.12
P-value4	0.062	0.022*	< 0.001*	0.173	0.001*

Data are expressed as the mean (SD). P was considered significant if < 0.05. TLC: total leucocyte count; ANC: absolute neutrophil count; CBC: complete blood count. P-value1: compared baseline with 1st month; P-value2: compared baseline with 2nd month; P-value3: compared baseline with the end of therapy; P-value4: compared baseline with 3 months after therapy.

The mean PLT count decreased significantly at the end of treatment compared to baseline in both groups ($p < 0.001$ and $p = 0.005$, respectively). The percent decrease in the mean PLT count was significantly higher in Group 1 than in Group 2 ($p = 0.032$).

The mean albumin level significantly decreased at the end of treatment in both groups ($p < 0.001$ for each). However, there was no significant difference between the groups in the percent decrease in the mean albumin level ($p > 0.05$). In both groups, we found a significant decrease in the mean ALT and AST levels at the end of treatment ($p < 0.001$). However, there was no significant difference between the groups ($p > 0.05$).

Regarding the mean total bilirubin level, there was a significant increase in both groups at the end of treatment ($P < 0.001$). There was no significant difference between the groups in the percent change ($p > 0.05$). However, the percent increase in the mean indirect bilirubin level was significantly higher in Group 2 than in Group 1. At the end of the treatment, there was no change in the mean INR in Group 1, but there was a significant increase in the mean INR in Group 2. However, there was no significant difference between the groups in the mean INR.

In the current study, the mean baseline FIB-4 score in Group 1 was significantly higher than that in Group 2 ($p < 0.001$).

There was improvement in the FIB-4 score at end of the treatment in both groups when compared to the baseline score. The percent improvement in the FIB-4 score was higher in Group 1 than in Group 2, but the difference was not statistically significant ($p > 0.05$). The improvement was maintained 3 months after the end of treatment (SVR) in both groups: the mean value of the FIB4 score at SVR was 2.88 in Group 1 and 2.39 in Group 2 ($p < 0.001$ both compared to baseline).

The most well-tolerated regimen was SOF, DAC and RBV for three months, and 39 patients (39%) developed minor adverse effects. Among those who received SOF and RBV for 6 months, 47 patients (47%) developed minor adverse effects ($p = 0.253$).

The most frequent adverse effect was fatigue, which occurred in 21 patients (21%) in Group 1 and 18 patients (18%) in Group 2 ($p = 0.295$). The second most common side effect was headache, which occurred in 10 patients (10%) in Group 1 and 8% of patients in Group 2.

We noticed in the current study that anaemia was the most frequently observed haematological abnormality during the treatment period, and a low Hb level below 10 g/dl was observed more frequently in Group 1 (28%) than in Group 2 (15%) ($p = 0.025$). Only 2 patients in our study stopped RBV treatment (one patient in Group 1 and the other in Group 2) because of a decrease in the Hb level to less than 8.5 g/dl.

DISCUSSION

In Group 1 patients who received SOF/RBV for 6 months, the ETR was 98%, and the SVR was 75%. This finding was in agreement with the results of two studies performed by Elsharkawy *et al* (2017), in which the SVR12 rate was 78.6% among 70 HCV-infected Egyptian patients (64.3% had compensated cirrhosis) treated with SOF/RBV for 24 weeks[11]. In another study, SVR12 was achieved in 76% of 3462 cirrhotic patients treated with SOF/RBV for 24 weeks[12]. However, the SVR 12 rate in Group 1 was lower than that reported by Doss *et al*[13], who evaluated SOF/RBV in treatment-naive and treatment-experienced Egyptian patients with HCV genotype 4 infection for either 12 or 24 weeks. The SVR12 in treatment-naive patients with cirrhosis was higher in the group treated for 24 weeks (3/3, 100%) vs. the group treated for 12 weeks (2/3, 67%).

Group 2 received (SOF/DAC/RBV). In this group, 100 patients (100%) achieved ETR, and 96 patients (96%) achieved SVR. These findings were in agreement with the study by El-Khayat *et al*[14], who reported that the ETR rate was 94.2%, while the SVR rate at week 12 post-treatment in their study was 94%, which was near to our results.

The ETR rate in Group 2 was in agreement with the ETR rate of 100% in 40 HCV G4 infected patients (35.9% of them with cirrhosis at baseline) treated with SOF/DCV ± RBV reported by Babatin *et al*[15].

The most prominent change in CBC parameters during treatment with SOF-containing regimens was the significant decrease in Hb levels in both groups. The mean difference between the pretreatment Hb level and that at the end of treatment was -1.65 g/dl in Group 1 and -1.31 g/dl in Group 2. The decrease in the mean Hb level in Group 2 was lower than that in Group 1, which may be explained by the use of weight-based RBV dosing in Group 1, while patients in Group 2 initially received low-dose RBV (600 mg/day) with a step-wise dose increase. In the current study, anaemia with an Hb level < 10 g/dl developed in 28 patients (28%) in Group 1 and 15 patients (15%) in Group 2.

This finding was not surprising due to the well-known effect of RBV therapy to cause haemolytic anaemia. The NIAID SPARE trial evaluated the use of SOF with either low-dose (600 mg daily) or weight-based RBV dosing in patients with chronic HCV genotype 1 for 24 weeks. The trial demonstrated that 32% (8/25) of those who received weight-based RBV became anaemic (Hb ≤10.9 g/dl), and 5 subjects (20%) required dose reductions, while only 16% (4/25) of those who received low-dose RBV became anaemic, and 3 patients (12%) required dose reduction[16]. Ruane *et al*[17] evaluated treatment-naive and previously treated Egyptian HCV genotype 4 patients with

Table 5 Changes in liver function tests in Group 2 patients during the study period.

Time of follow-up	ALT (0-41 U/L)	AST (0-38 U/L)	Bilirubin (0-1 mg/dl)	Indirect bilirubin (0-0.75 mg/dl)	Albumin (3.5-5 g/dl)	INR (0.9-1.22)
Baseline	64.05 ± 32.99	62.81 ± 28.11	0.98 ± 0.37	0.57 ± 0.20	3.66 ± 0.48	1.20 ± 0.15
1st month	42.43 ± 20.12	40.27 ± 14.87	1.24 ± 0.41	0.78 ± 0.29	3.57 ± 0.42	1.21 ± 0.14
2nd month	34.61 ± 14.22	34.21 ± 10.71	1.28 ± 0.43	0.84 ± 0.31	3.58 ± 0.41	1.21 ± 0.14
End of therapy	32.65 ± 11.60	31.91 ± 7.99	1.25 ± 0.38	0.81 ± 0.24	3.58 ± 0.40	1.21 ± 0.14
3 months after therapy	29.96 ± 9.59	30.13 ± 7.80	1.00 ± 0.34	0.60 ± 0.19	3.68 ± 0.41	1.18 ± 0.15
P-value1	< 0.001*	< 0.001*	< 0.001*	0.003*	< 0.001*	0.005*
P-value2	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	0.004*
P-value3	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	0.032*
P-value4	< 0.001*	< 0.001*	0.024*	< 0.001*	0.18	< 0.001*

Data are expressed as the mean (SD). P was considered significant if < 0.05. ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio. P-value1: compared baseline with 1st month; P-value2: compared baseline with 2nd month; P-value3: compared baseline with the end of therapy; P-value4: compared baseline with 3 months after therapy.

daily SOF 400 mg and weight-based RBV therapy for 12 weeks (n = 31) or 24 weeks (n = 29). Four patients, all in the 24-week group (14%), had Hb levels < 10 g/dl, but none had Hb levels < 8.5 g/dl.

In a study reported by Abdel-aziz *et al*[18], 8 (18.4%) of 40 Egyptian patients developed low Hb levels < 10 g/dl during treatment with SOF (400 mg), DAC (60 mg) and RBV (600-1000 mg in divided doses according to patient tolerance).

In the present study, we found a significant decrease in the PLT count during the treatment period in both groups. The percent decrease in the mean PLT count was higher in Group 1 than in Group 2. Additionally, we found a significant decrease in the WBC count during treatment in both groups.

Tong *et al*[19] allocated 128 patients with chronic HCV infection (30.5% had compensated cirrhosis) into 4 groups. In the group that was treated with SOF/RBV for 24 weeks, thrombocytopenia and neutropenia developed only in 14.5% (9/62) and 19.4% (12/62) of patients, respectively.

In the current study, the decrease in the mean PLT count in Group 1 patients was in agreement with the results reported by Elsharkawy *et al*[11], who found a significant decrease in the PLT count in 45 Egyptian patients with cirrhosis during therapy with SOF/RBV for 24 weeks, with a mean difference in the PLT count of -11.87×10^3/mm^3 between pretreatment and the end of treatment. However, in this study, 12 patients with cirrhosis who received SOF/DAC ± RBV developed a non-significant increase in the PLT count, with a mean difference in the PLT count of 34.4×10^3/mm^3 between pretreatment and the end of treatment, which was not in agreement with the results of the present study.

In our study, the decrease in the mean WBC count in Group 1 was in agreement with the results reported by Elsharkawy *et al*[11], who found a significant decrease in the WBC count in 8 Egyptian patients with cirrhosis treated with SOF/RBV for 24 weeks with a mean difference in the mean WBC count of -1.84×10^3/mm^3 between pretreatment and the end of treatment. However, in the same study 17 patients with cirrhosis treated with SOF/DAC ± RBV had a non-significant increase in the mean WBC count of 0.18×10^3/mm^3 at the end of treatment compared to the pretreatment mean WBC count, which was inconsistent with our results.

The results of the present study were inconsistent with the results reported by Abd-Elsalam *et al*[20], who studied 2400 Egyptian patients with HCV-related Child A and B liver cirrhosis (96.6% were treatment-naive) and found a non-significant increase in the mean PLT and WBC counts at the end of 24 weeks of SOF/RBV therapy of 12×10^3/mm^3 and 0.2×10^3/mm^3, respectively.

In both groups in our study, we found a significant decrease in the mean levels of transaminases (AST and ALT) during treatment. This finding was in agreement with those of Elsharkawy *et al*[11], who reported that ALT and AST levels were significantly decreased in 64 patients (among them, 28% had cirrhosis) treated with SOF/DAC ± RBV for 12 weeks and in 70 patients (among them, 64.3% had cirrhosis) treated with SOF/RBV for 24 weeks. Additionally, this finding was in agreement with those of Abd-Elsalam *et al*[20], who found significant decreases in ALT and AST levels in 2400 patients with cirrhosis treated with SOF/RBV for 6 months, and the mean difference in the ALT and AST levels were -23 U/L and -24 U/L, respectively, between pretreatment and the end of treatment.

At the end of treatment in both groups in the current study, we found a significant increase in the mean total bilirubin and indirect bilirubin levels compared to the mean pretreatment levels. This finding can be explained by RBC haemolysis due to RBV, which leads to an increase in the mean indirect bilirubin level. This finding

Table 6 Changes in laboratory data and the FIB4 score at the end of treatment compared to baseline in the studied groups.

Variables (normal range)		Group 1	Group 2	P-value1
Hb (12-17 g/dl)	Baseline	12.88 ± 1.09	12.98 ± 1.35	
	End of treatment	11.23 ± 1.05	11.66 ± 1.28	
	Mean difference	-1.65 ± 0.95	-1.31 ± 0.94	0.009*
	Percent difference	-12.62 ± 6.98	-9.92 ± 6.72	0.006*
	P-value2	< 0.001*	< 0.001*	
TLC (4-11 × 10^3/mm^3)	Baseline	5.07 ± 1.33	5.47 ± 1.55	
	End of treatment	4.09 ± 1.12	4.74 ± 1.20	
	Mean difference	-0.98 ± 0.85	-0.74 ± 0.79	0.030*
	Percent difference	-18.41 ± 14.43	-12.13 ± 11.94	0.001*
	P-value2	< 0.001*	< 0.001*	
ANC (2-7 × 10^3/mm^3)	Baseline	2.52 ± 0.70	2.66 ± 0.75	
	End of treatment	2.03 ± 0.55	2.28 ± 0.57	
	Mean difference	-0.49 ± 0.47	-0.38 ± 0.42	0.097
	Percent difference	-18.35 ± 14.93	-12.70 ± 13.41	0.005*
	P-value2	< 0.001*	< 0.001*	
Platelets (150-450 × 10^3/mm^3)	Baseline	128.75 ± 31.57	147.69 ± 37.67	
	End of treatment	124.65 ± 31.38	145.30 ± 36.46	
	Mean difference	-4.10 ± 8.23	-2.39 ± 8.27	0.131
	Percent difference	-3.18 ± 6.81	-1.34 ± 6.05	0.032*
	P-value2	< 0.001*	0.005*	
Creatinine (0.5-1.2 mg/dl)	Baseline	0.84 ± 0.16	0.87 ± 0.13	
	End of treatment	0.86 ± 0.10	0.85 ± 0.09	
	Mean difference	0.01 ± 0.09	-0.02 ± 0.09	0.005*
	Percent difference	2.90 ± 10.35	-0.87 ± 9.92	0.004*
	P-value2	0.199	0.12	
ALT (0-41 U/L)	Baseline	58.30 ± 21.92	64.05 ± 32.99	
	End of treatment	30.09 ± 8.75	32.65 ± 11.60	
	Mean difference	-28.21 ± 21.45	-31.40 ± 28.01	0.829
	Percent difference	-41.86 ± 23.0	-39.51 ± 27.60	0.851
	P-value2	< 0.001*	< 0.001*	
AST (0-38 U/L)	Baseline	69.25 ± 22.97	62.81 ± 28.11	
	End of treatment	34.61 ± 8.38	31.91 ± 7.99	
	Mean difference	-34.64 ± 21.60	-30.90 ± 25.30	0.107
	Percent difference	-45.73 ± 17.52	-41.58 ± 22.67	0.277
	P-value2	< 0.001*	< 0.001*	
Bilirubin (0-1 mg/dl)	Baseline	1.10 ± 0.43	0.98 ± 0.37	
	End of treatment	1.37 ± 0.41	1.25 ± 0.38	
	Mean difference	0.27 ± 0.28	0.27 ± 0.20	0.869
	Percent difference	33.57 ± 39.98	34.03 ± 32.24	0.407
	P-value2	< 0.001*	< 0.001*	
Indirect bilirubin (0-0.75 mg/dl)	Baseline	0.67 ± 0.23	0.57 ± 0.20	
	End of treatment	0.89 ± 0.25	0.81 ± 0.24	
	Mean difference	0.22 ± 0.20	0.24 ± 0.19	0.006*
	Percent difference	37.10 ± 47.30	58.35 ± 45.03	< 0.001*
	P-value2	< 0.001*	< 0.001*	
Albumin (3.5-5 g/dl)	Baseline	3.42 ± 0.38	3.66 ± 0.48	
	End of treatment	3.37 ± 0.35	3.58 ± 0.40	
	Mean difference	-0.05 ± 0.13	-0.08 ± 0.16	0.086
	Percent difference	-1.31 ± 3.94	-1.93 ± 4.24	0.286
	P-value2	< 0.001*	< 0.001*	
INR (0.9-1.22)	Baseline	1.26 ± 0.13	1.20 ± 0.15	
	End treatment	1.26 ± 0.13	1.21 ± 0.14	
	Mean difference	0.0 ± 0.04	0.01 ± 0.05	0.115
	Percent of difference	0.34 ± 3.39	1.26 ± 4.77	0.101
	P-value2	0.401	0.032*	
FIB-4 score	Baseline	4.15 ± 1.40	3.48 ± 1.92	< 0.001
	End of treatment	2.99 ± 0.95	2.47 ±1.09	
	Mean difference	-1.16 ± 0.94	-1.01 ± 1.35	0.077
	Percent difference	-25.46 ± 17.63	-22.68 ± 30.44	0.815
	P-value2	< 0.001*	< 0.001*	

Data are expressed as the mean (SD). P was considered significant if < 0.05. ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; FIB-4: fibrosis index based on four factors; Hb: haemoglobin; INR: international normalized ratio; TLC: total leucocyte count. Group 1: patients received sofosbuvir and ribavirin for six months; Group 2: patients received sofosbuvir, daclatasvir and ribavirin for three months. P-value1: Compared between Group 1 and Group 2; P-value2: Compared baseline with end treatment in each group.

was in agreement with those of Abd-Elsalam *et al*[20], who found a significant increase in the mean total bilirubin level of 1.7 mg/dl during treatment of 2400 Egyptian patients with cirrhosis treated with SOF/RBV for 6 months. However, this finding was not in agreement with those of Elsharkawy *et al*[11], who reported that 12 Egyptian patients with cirrhosis who received SOF/DAC ± RBV for 12 weeks and 37 Egyptian patients with cirrhosis who received SOF/RBV for 24 weeks developed a non-significant increase in the mean total bilirubin level at the end of treatment.

In the current study, we found a significant change in the mean albumin level at the end of treatment of -0.05 g/dl and -0.08 g/dl in Groups 1 and 2, respectively. This finding was similar to those of Elsharkawy *et al*[11], who found a significant decrease in the mean albumin level of 0.03 g/dl at the end of treatment compared to mean pretreatment level in 14 Egyptian patients with cirrhosis treated with SOF/DAC ± RBV for 12 weeks. However, in that study, 31 Egyptian patients with cirrhosis who received SOF/RBV for 24 weeks had a significant increase in the mean albumin level at the end of the treatment of 0.035 g/dl compared to the mean pretreatment albumin level, which is not in agreement with the results of the present study.

Our results were inconsistent with the results reported by Abd-Elsalam *et al*[20], who found a non-significant decrease in the mean albumin level of 1 g/dl in 2400 Egyptian patients with Child A and B cirrhosis (96.6% were treatment-naive) at the end of 24 weeks of SOF/RBV therapy. Deterding *et al*[21] found a significant increase in the albumin level during treatment of 80 patients with cirrhosis treated with SOF/RBV, SOF/SIM ± RBV or SOF/DAC ± RBV for 24 weeks, and this increase continued until the end of their study, which also was inconsistent with the results of the current study.

At the end of the treatment, we found a significant prolongation in the mean INR in Group 2 of 0.01 compared to the pretreatment INR, but no change was noted in the mean INR in Group 1. This finding was in accordance with those of Elsharkawy *et al*[11], who noted that in 108 patients with cirrhosis treated with SOF/RBV, SOF/SIM or SOF/DAC±RBV, the mean INR was significantly increased by 0.1 at the end of treatment, representing probable worsening of liver function.

In the present study, we found an improvement in the FIB-4 score at the end of treatment in both groups, which continued until SVR in both groups ($P < 0.001$ for both). This result is in agreement with the results of Elsharkawy *et al*[22], who reported a significant decrease in the mean FIB-4 score at SVR12 in Egyptian patients with cirrhosis who were treated with SOF/SIM, SOF/RBV or SOF/DAC ± RBV.

Fatigue and headache were the most commonly recorded complications in the studied groups during treatment. This finding was in agreement with those of Doss *et al*[13], who found that during treatment of 51 Egyptian chronic hepatitis C (CHC) patients (18% of them had cirrhosis) treated with SOF/RBV for 24 weeks, fatigue and headache were the most common complications reported in 14 patients (27%) and 11 patients (22%), respectively. Additionally, Elsharkawy *et al*[23] noted that fatigue and headache were the most commonly reported complications during the treatment of 139 Egyptian patients with chronic HCV (among them 40.5% had cirrhosis) with SOF/DAC ± RBV for 12 or 24 weeks and occurred in 30% and 24% of the patients, respectively.

CONCLUSION

SOF/DAC/RBV was the most efficacious and well-tolerated treatment regimen. The mean Hb level and PLT count decreased significantly at the end of treatment in both groups, and the percent decrease was significantly higher in those who received SOF and RBV for 24 weeks than in those who received SOF, DAC and RBV for 12 weeks.

Anaemia was the most frequently observed haematological abnormality during the treatment period, and a low Hb level below 10 g/dl was observed more frequently in those who received SOF and RBV for 24 weeks (28%). In patients who achieved SVR, there was improvement in liver function parameters and the FIB4 score at the time of SVR12 compared to baseline values in both groups.

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