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

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[6] found that globally, the prevalence and number of people with anti-HCV were 2.8% and >185 million, respectively. Gower et al[7] 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[8] and is durable, as < 1% of individuals who achieved an SVR subsequently tested positive for serum HCV RNA[9].

Treatment of chronic hepatitis C with pegylated interferon-alpha (PEG-a) 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[10].

A better understanding of the HCV life cycle and viral enzymes that are potential antiviral targets[11] has led to the establishment of a number of new direct-acting antiviral agents (DAAs) directed against viral proteins[12].

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[13].

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-naïve). 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-naïve 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[14] 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 Francisius, 2015[15]. 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/m²) than in Group 2 (26.95 ± 4.21 kg/m²) (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).

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

The mean total leucocyte 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 LFT levels was maintained until SVR.

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Table 1: Baseline laboratory data of the studied groups.

| Variables (normal range) | Group 1 (n = 100) Mean ± SD | Group 2 (n = 100) Mean ± SD | p-value4 |
|--------------------------|-----------------------------|-----------------------------|----------|
| 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 (0.075 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 (0.9-1.2)            | 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 × 10³/mm³)     | 5.07 ± 1.33                 | 5.47 ± 1.55                 | 0.093    |
| ANC (2–7 × 10³/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 × 10³/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.

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

| Time of follow-up | TLC (4–11 × 10³/mm³) | ANC (2–7 × 10³/mm³) | Haemoglobin (12-17 g/dl) | Platelets (150-450 × 10³/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               |
| 5 months after therapy | 4.91 ± 1.01      | 2.39 ± 0.49          | 12.66 ± 0.87             | 127.06 ± 50.18               | 0.85 ± 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*                      | --                        |
| 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.
Changes in liver function tests in Group 1 patients during the study period.

Table 3

| 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          | 1.62 ± 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        | 53.83 ± 11.09  | 59.10 ± 11.39 | 1.53 ± 0.51          | 0.99 ± 0.32                      | 3.34 ± 0.36          | 1.28 ± 0.13     |
| 3rd month        | 54.15 ± 10.44  | 57.08 ± 10.35 | 1.43 ± 0.46          | 0.90 ± 0.28                      | 3.35 ± 0.36          | 1.27 ± 0.13     |
| 4th month        | 31.70 ± 9.77   | 56.40 ± 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*      | < 0.001*             | 0.799                            | < 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.

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

Table 5

| 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         | 5.47 ± 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*              | < 0.001*             | < 0.001*                | < 0.001*                        | < 0.001*                 |
| P-value2         | < 0.001*              | < 0.001*             | < 0.001*                | < 0.001*                        | 0.361                    |
| P-value3         | < 0.001*              | < 0.001*             | < 0.001*                | < 0.001*                        | 0.05*                    |
| 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.
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. In another study, SVR12 was achieved in 76% of 3462 cirrhotic patients treated with SOF/RBV for 24 weeks. However, the SVR 12 rate in Group 1 was lower than that reported by Doss et al., 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., 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.

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. Ruiz et al. evaluated treatment-naive and previously treated Egyptian HCV genotype 4 patients with

| 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*  < 0.001*  < 0.001*  < 0.001*  < 0.001*  < 0.001*  < 0.001*  < 0.001*  < 0.001*  < 0.001*  < 0.001*  < 0.001*  < 0.001*

Data are expressed as the mean (SD). It 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.\(^{(21)}\), who found a significant decrease in the PLT count in 45 Egyptian patients with cirrhosis treated with therapy with SOF/RBV for 24 weeks, with a mean difference in the PLT count of \(-1.84 \times 10^5\) mm\(^3\) between pretreatment and the end of treatment. However, in the current 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 \(3.4 \times 10^5\) 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.\(^{(21)}\), who found a significant decrease in the WBC count in 45 Egyptian patients with cirrhosis treated with therapy with SOF/RBV for 24 weeks, with a mean difference in the mean WBC count of \(-1.84 \times 10^5\) mm\(^3\) between pretreatment and the end of treatment. However, in the same study 17 patients with cirrhosis treated with SOF/RBV + RBV had a non-significant increase in the mean WBC count of \(0.18 \times 10^5\) 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-naïve) and found a non-significant increase in the mean PLT and WBC counts at the end of 24 weeks of SOF/RBV therapy of \(12 \times 10^9\) mm\(^3\) and 0.2 \(10^9\) 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.\(^{(21)}\), 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 was in agreement with the results reported by Tong et al.\(^{(19)}\), who found a significant decrease in the WBC count in 45 Egyptian patients with cirrhosis treated with therapy with SOF/RBV for 24 weeks, with a mean difference in the mean WBC count of \(-1.84 \times 10^5\) mm\(^3\) between pretreatment and the end of treatment. However, in the same study 17 patients with cirrhosis treated with SOF/RBV + RBV had a non-significant increase in the mean WBC count of \(0.18 \times 10^5\) 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 Elsharkawy et al.\(^{(21)}\), who studied 4200 Egyptian patients with HCV-related Child A and B liver cirrhosis (96.6% were treatment-naïve) and found a non-significant increase in the mean PLT and WBC counts at the end of 24 weeks of SOF/RBV therapy of \(12 \times 10^9\) mm\(^3\) and 0.2 \(10^9\) mm\(^3\), respectively.

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was in agreement with those of Abd-Elsalam et al., 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., 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., 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., 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. 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., 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., 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., 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. 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 FIB-4 score at the time of SVR12 compared to baseline values in both groups.

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