Sohag University Sohag Medical Journal Faculty of Medicine

Efficacy, Safety, and Biochemical Response of Sofosbuvir and Daclatasvir Combination in Chronic Hepatitis C Treated Patients in Sohag Governorate

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Abstract:

Background: Worldwide use of direct-acting antiviral agents (DAAs) is nowadays the standard method for the treatment of HCV infection. Different researches reported that DAAs have an acceptable safety profile and sustained virological response (SVR) rate compared with previous treatment combinations containing interferon. Therefore, our study aimed to estimate the rate of SVR in patients treated with sofosbuvir-based regimens in Sohag Governate and to assess the adverse events (AEs) and the biochemical response to therapy in the studied population.

Patients and Methods: Our study was a prospective one that included 135 patients eligible for treatment with sofosbuvir-based regimens. Patients were categorized into two different groups: Group one received sofosbuvir with daclatasvir combination and group two received sofosbuvir plus daclatasvir with ribavirin. The SVR12 and adverse events of the treatments were evaluated. Liver function tests were assessed at the start of treatment, at 4 weeks, at the end of therapy and at 12-week after completing the therapy.

Results: The SVR rate at 12-week after completing the therapy was nearly equal in both groups (98.5%). The most frequently reported side effects were fatigue and headache. Liver function tests were significantly improved at SVR12.

Conclusion: Sofosbuvir plus daclatasvir ± ribavirin were highly effective and adequately tolerated.

Keywords: SVR12, Adverse events, Biochemical response.

1. Introduction:

Chronic hepatitis C virus (HCV) is one of the most frequently reported infection, affecting about seventy-one million people all over the world [(1)]. Egypt is considered to have the highest prevalence of chronic hepatitis C (CHC) in the world. In 2008, the Demographic Health Survey documented that the prevalence of anti-HCV antibodies in the age groups 15–59 years was 14.7%. However, in 2015, the reported HCV prevalence was 10% [(2)].

The aim of CHC management is to reach SVR, which is known as an undetectable level of viremia at 12 or 24 weeks after completing the therapy [(3)]. In 2011, a major change in the management of CHC was noticed after the appearance of DAAs.

Among DAAs, sofosbuvir with daclatasvir combination showed promising results [(4)]. Sofosbuvir has pan-genotypic activity by inhibiting

HCV NS5B polymerase. It was approved in December 2013. Daclatasvir inhibits the HCV NS5A replication complex and was approved in July 2013 [5].

Several studies reported that the efficacy of sofosbuvir with daclatasvir ±ribavirin was high across different HCV genotypes [6-8]. Several Egyptian studies in patients with CHC infection showed similar results [1,4,5]. So, in the current study, we aimed to estimate the effectiveness, the adverse events (AEs) and the biochemical response to sofosbuvir containing therapy in the studied population.

2. Patients and Methods

The present study was a prospective one that included one hundred thirty-five chronic HCV infected individuals. They were recruited from Tropical Medicine and Gastroenterology Outpatient Clinic in Sohag University Hospital during the period from July 2016 to January 2018.

The treatment protocol was in line with the protocol of the National Program for the treatment of CHC in Egypt provided by the Ministry of Health (2015). The patient inclusion criteria were: HCV RNA positive patient, Age 18–75 years. Exclusion criteria were: HBV co-infection, INR more than 1.7, serum albumin level less than 2.8 g/dl, total serum bilirubin level more than 3 mg/dl, HCC and extra-hepatic malignancy, uncontrolled diabetes mellitus (HbA1c>9%), being pregnant or being unable to adopt contraceptive measures.

Patients were classified into two groups: The first group (N= 68) included: treatment-naive patients and had the following laboratory parameters (serum albumin more than or equal to 3.5 g/dl, total bilirubin less than or equal to 1.2 mg/dl, INR less than or equal to 1.2, platelet counts more than or equal to 150,000 mm^3. They received dual therapy (sofosbuvir (400 mg once daily) plus daclatasvir (60 mg once daily)) for twelve weeks. The second group (N= 67) included: Peg-IFN treatment-experienced patients and patients with one or more of the following laboratory parameters (serum albumin less than 3.5 g/dl, total bilirubin more than 1.2 mg/dl, INR more than 1.2, platelet counts less than 150000 mm^3). They received triple therapy (sofosbuvir (400 mg once daily) plus daclatasvir (60 mg once daily)) with ribavirin (according to the body weight in kilograms up to 1000 mg/day)) for twelve weeks [1]. Our study protocol was accepted by the Ethics Committee of the Sohag Faculty of Medicine. Informed written consent was taken from all patients included in the present study.

The following were done for all patients:

1) **Full history taking and clinical evaluation** of manifestation of liver cell failure as jaundice, ascites, palmar erythema, and spider naevi.
2) **Laboratory investigations:** Complete blood count, **liver function tests:** serum albumin, Prothrombin time and concentration, ALT, AST, **Fasting blood glucose**: **HBA_{1c}:** If the patient was diabetic, **Hepatitis markers**: Hbs antigen and Anti-HCV antibodies, HCV RNA assessment.
3) **Abdominal ultrasonography**: Abdominal ultrasound was performed for all patients using the ultrasound system (Siemens S2000 VC25B, AG, Germany) using a 3.5-5 MHz convex transducer. Longitudinal, transverse and intercostal scans were performed for assessment of liver size, surface, echogenicity, ascites, presence of hepatic focal lesions, the size of the spleen, portal vein diameter.
4) **Liver stiffness measurement (LSM) using shear wave elastography**:

The examination was performed using the ultrasound system (Siemens S2000 VC25B, AG, Germany) with a convex broadband probe. This technique generates shear waves inside the liver using radiation force from a focused ultrasound beam. The ultrasound machine monitors the shear wave propagation using a doppler like ultrasound technique and measures the velocity of the shear wave. The shear wave velocity (SWV) is displayed in meters per second (m/sec). The degree of fibrosis evidenced by LS using SWV was stratified to the corresponding the METAVIR score with the following cutoffs: F0 (0.8: 1.19), F1 (1.2: 1.34), F2 (1.35: 1.60), F3 (1.61: 2), F4 > 2 [9].

5) **Patients assessment:** Patients were assessed during treatment by liver function tests and CBC at the start of treatment, at 4 weeks, at the end of therapy and at 12-week after completing the therapy.
6) **Endpoint of treatment:** HCV RNA estimation was done at the end of therapy and at 12-week after completing the therapy. The endpoint of treatment of the study was SVR12, defined as an undetectable level of viremia (<15 IU/ml) at the end of therapy and at 12-week after completing the therapy. Viral relapse was an undetectable level of viremia (<15 IU/ml) at the end of therapy, but detectable levels of viral RNA (>15 IU/ ml) at 12-week after completing the therapy [1].
7) **Statistical analysis:** Data were analyzed using STATA version 14.2 (Statistical Software: Release 14.2 College Station, TX: Stata Corp LP). Quantitative data were viewed as mean, standard deviation, median, and range. ***Kruskal Wallis*** was used for comparing three or more groups when the data were not normally distributed. Qualitative data were viewed as numbers and percentages. ***A chi-square*** test was used for comparison of percentages between different groups. A ***P value*** of less than 0.05 was considered significant.

3. Results of the Study

One hundred thirty-five patients with chronic HCV who were eligible for treatment with sofosbuvir-based combinations were included in the present study**.** The patient's demographic and clinical data were shown in **(Table 1)**. All patients received treatment had an undetectable level of viral load after completing the treatment. The SVR12 rate was nearly equal in patients receiving dual and triple therapy (98.5%) **(Table 2).** The two relapsed patients were males. They were treatment naïve. One of them had an advanced stage of fibrosis and the other one had cirrhosis **(Table 3).**

The mean serum level of total bilirubin, AST and ALT were significantly reduced after SVR12 (P = 0.0002, 0.0001, 0.0001, respectively) **(Table 4).** Also, there was a significant improvement in the mean level of serum albumin, prothrombin time, prothrombin concentration and INR after SVR12 ($P \leq 0.0001$) **(Table 5).**

Fatigue and headache were the most frequently reported adverse effects of SOF-based combinations in studied patients. These adverse effects were more frequent in those receiving triple treatment, but without statistically significant difference **(Table 6)**.

Table (1): Some demographic and clinical data of **the studied population**

Characteristics	Dual regimen group, N=68	Triple regimen group, N=67	P value
Age (years) Mean ± SD	49.38±12.72	50.29±11.26	0.66
Gender: Male/Female	50 (73.5%) / 18 (26.5%)	40 (59.7%) / 27 (40.3%)	0.14
BMI (kg/m^2): Mean ± SD	27.32±2.57	27.49±2.41	0.69
Cirrhotic patients: n (%)	0(0%)	31 (46.3%)	0.000
Diabetic patients: n (%)	8 (11.8%)	13 (19.4%)	0.24
Hypertensive patients: n (%)	6 (8.8%)	4 (5.9%)	0.74

Table (2): Treatment response in the studied patients

Treatment data	Summary statistics
Type of treatment: n (%), Dual/Triple	68 (50.37%)/67 (49.63%)
ETR: End of treatment response: n(%)	135 (100%)
Dual treatment: n (%) SVR 12/Relapser	67(98.52%)/1(1.48%)
Triple treatment: n (%) SVR 12/ Relapser	66 (98.50%) / 1 (1.5%)

N%: Number, percentage Dual: sofosbuvir with daclatasvir
Triple: sofosbuvir, daclatasvir with ribavirin
SVR12: Sustained virological response at 12 weeks after completing the treatment

Table (3): Criteria of relapsed cases

Characteristics	Case 1	Case 2
Age (years)	46	55
Gender	Male	Male
Body mass index(kg/m2)	27	26
Previous treatment	Treatment naive	Treatment naive
Type of treatment	Triple	Dual
PCR at baseline (IU/ml)	9.6×106	79244
PCR at relapse (IU/ml)	21.6×106	158245
Shear wave velocity (m/sec)	2.4 (F4)	1.69 (F3)

Table (4): Laboratory data that measured at baseline, 4 weeks, end of therapy, and at SVR12.

Investigation	Baseline	4 weeks	End of therapy	SVR12	P-value
WBCs (10^9/l) Mean ± SD	6.35±2.54	6.25±2.11	6.10±2.05	6.16±1.93	0.58
Hamoglobin (g/dl) Mean ± SD	13.92±1.69	12.97±1.76	12.50±1.40	13.87±1.86	0.72
Platelets (10^9/l) Mean ± SD	200.58±74.51	197.25±63.71	197.06±64.86	206.26±72.25	0.22
T.bilirubin(mg/dl)Mean± SD	0.85±0.32	0.96±0.53	0.87±0.41	0.75±0.32	0.0002***
ALT(IU/l) Mean ± SD	46.4±34.55	29.38±17.48	23.31±12.76	19.40±11.20	<0.0001***
AST(IU/l) Mean ± SD	46.20±35.88	31.70±17.90	27.13±16.26	23.12±12.21	<0.0001***

SD: Standard deviation *** = highly significant
ALT: Alanine aminotransferase AST: Aspartate aminotransferase
SVR12: Sustained virological response at 12 weeks after completing the treatment

Table (5): Other laboratory data that measured at baseline and at SVR12

Investigation	Baseline	SVR12	P-value
Serum albumin (g/dl) Mean ± SD	4.12±0.53	4.33±0.50	<0.0001***
Prothrombin time (sec) Mean ± SD	12.76±1.40	12.16±1.26	<0.0001***
Prothrombin concentration (%) Mean ± SD	87.79±12.99	91.26±11.25	0.0001***
INR Mean ± SD	1.08±0.14	1.01±0.11	<0.0001***

SVR12: Sustained virological response at 12 weeks after completing the treatment
*** = highly significant INR: International normalized ratio
SD: Standard deviation Sec: second

Table (6): Adverse events of sofosbuvir-based regimens in studied patients

Adverse events of treatment	Dual therapy group, N=68	Triple therapy group, N=67	Total N=135	P-value
Fatigue	25 (36.8%)	34 (50.7%)	59 (43.7%)	0.12
Headache	12 (17.6%)	18 (26.9%)	30 (22.22%)	0.22
Nausea and epigastric pain	9 (13.2%)	12 (17.9%)	21 (15.6%)	0.49
Itching	1 (1.5%)	0 (0%)	1 (0.74%)	1
Decreased appetite	1(1.5%)	2 (3%)	3 (2.2%)	0.62
Diarrhea	2 (2.9%)	3 (4.5%)	5 (3.7%)	0.68
Lower limb edema	0 (0%)	1(1.5%)	1 (0.74%)	1
Serious adverse events or death	0 (0%)	0 (0%)	0 (0%)	0

4. Discussion

In the present study, the SVR12 was nearly equal in both groups treated with dual and triple therapy (98.5%). Our result was in agreement with some studies that reported little difference in the response rate between dual and triple therapy as shown by **Omar et al.** [10] and **Shiha et al.** [11].

On the other side, **Abdel Moneim et al.** [1] and **Herzer et al.** [7] reported a significant difference in the response rate between patients treated with dual and triple therapy. The difference in the response rate between our study and previous studies might be explained by the difference in many factors as patients' characteristics, the number of cirrhotic patients and the stage of liver fibrosis.

In our study, the relapsed patients had an advanced stage of hepatic fibrosis and cirrhosis. Our results also were in line **with Welzel et al.** [12] who reported that most relapsed patients had more advanced liver fibrosis.

On evaluating the hematological changes during treatment, we found a decrease of hemoglobin (Hb) level during treatment follow up with normalization of Hb levels at SVR12**.** Also**, Bernuth et al.** [13] and **Swifee et al.** [14] showed that during follow up, Hb decreased from the baseline level but, an increase to the baseline levels was documented at 12 weeks after completing the treatment. Also, our result revealed an increase in platelet level at SVR12. This was in agreement with **Swifee et al.** [14]; **Van der Meer et al.** [3] **and Elsharkawy et al.** [15].

In the current study, we found a significant decrease in serum bilirubin levels and elevated transaminases (ALT and AST) at SVR12. Consistent with our findings, previous studies reported that treatment with SOF-based regimens resulted in a significant decrease in elevated transaminases [1, 4, 14]. Also, we noticed a significant improvement in serum albumin level and coagulation profile. In agreement with our results, several previous studies reported that there was a significant improvement in serum albumin, bilirubin and prothrombin time during treatment and at SVR12 [5,7, 13, 16, 17].

In the current study, we found that the most frequently reported side effects were headache and fatigue. The low incidence of AEs might be linked to a short duration of therapy when compared to IFN-containing therapy. Our results were in line with those of several previous studies as demonstrated by **Leroy et al.** [18] **; Shiha et al.** [11] and **Abdel Moneim et al**. [1].

No patient in our series stopped treatment due to severe adverse effects. on the other hand, some previous studies reported serious adverse events as acute kidney injury which was reviewed by **Sulkowski et al.** [6] and **Herzer et al**. [7]. Also, **Doss et al**. [19] concluded that two patients experienced severe AEs (cerebral ischemia, dyspnea). Also, **El-Khayat et al.** [20] noticed that ascites, GIT bleeding, hepatic encephalopathy, and renal affection were found mainly in child B cirrhotic patients. The severe AEs reported in several studies could be explained by certain hepatotoxic adverse effects caused by an unknown reaction to the combined therapy; though the relationship with the DAAs was not proven. Close monitoring is needed during therapy with DAAs; especially in cirrhotic patients [21].

5. Conclusion:

We noticed that sofosbuvir with daclatasvir ± ribavirin were highly effective and well-tolerated. Also, liver function tests were significantly improved at SVR12.

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