Comparative study between the efficacy of using sofosbuvir/daclatasvir and sofosbuvir/ledipasvir in treatment of hepatitis C virus in Egypt

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Background
Hepatitis C virus (HCV) infection is a global health care problem, with more than 170 million people infected worldwide. With the discovery of new direct-acting antiviral drugs, a new hope to get HCV cure has arisen. This work was designed to compare the efficacy between the use of sofosbuvir (SOF)/daclatasvir (DCV) and SOF/ledipasvir (LDV) in treatment of HCV.

Patients and methods
A total of 430 patients were enrolled into two groups: SOF/DCV group included 340 patients and SOF/LDV group included 90 patients. Each patient received treatment for 12–24 weeks. All patients were checked at each visit (at weeks 4, 8, 12, and 24) for the potential adverse events by a check-list questions, examinations, and laboratory tests. Check-list questions include headache, gastric upset, skin rash, and sleep disturbance.

Results
A total of 419 (97.4%) patients achieved sustained virologic response (SVR), and only 11 (2.5%) patients failed to achieve SVR. In SOF–DCV, 97.4%, and in SOF–LDV, 97.8% achieved SVR. Minor adverse events were mainly headache, sleep distribution, gastrointestinal tract disturbance, and skin rash, which were observed in 13.8% of patients in SOF–DCV group 20% in SOF–LDV group.

Conclusion
The use of the two regimens SOF/DCV and SOF/LDV yielded high success ratio for viral eradication with minimal tolerable adverse effects. These regimens of therapy have a great margin of safety with high efficacy.

Keywords:
gastroesophageal bleeding, liver cirrhosis, prophylaxis, questionnaire

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Introduction

Hepatitis C virus (HCV) infection is a global health care problem, with more than 170 million people infected worldwide. The pool of HCV infection ultimately ends with cirrhosis and the subsequent life-threatening complications [1]. With the discovery of new direct-acting antiviral drugs (DAAs), a new hope to get HCV cure has arisen. The infection is cured in more than 99% of patients who achieve a sustained virologic response (SVR) with a theoretical resolution of liver disease in patients without cirrhosis [2].

Nowadays, most of DAAs contain a sofosbuvir (SOF) molecule, which is the main backbone of DAA regimes. Several combinations that have emerged in the past 2 years have been recommended in the guidelines concerned with genotype 4, which is the most prevalent genotype in Egypt [3].

The ledipasvir (LDV)/SOF combination is a DAA that interferes with HCV replication and can be used to treat patients with genotypes 1a5 or 1b without pegylated-interferon or ribavirin [4].

Daclatasvir (DCV) inhibits the HCV nonstructural protein NS5A. Recent research suggests that it targets two steps of the viral replication process, enabling rapid decline of HCV RNA [5]. This work was designed to compare between the efficacy of using SOF/DCV and SOF/LDV in the treatment of HCV.

Patients and methods

Between January 2017 and January 2018, a prospective study was designed to enroll two groups of patients who were approved to have chronic HCV infection

and candidate to receive oral DAAs. Cases were recruited from dedicated centers for treatment of viral hepatitis at Assiut Center for Management of Viral Hepatitis (Ministry of Health) and El-Rajhy University Hospital. The study was approved by Ethical Committee of Faculty of Medicine, Assiut University. Written consents were obtained from all participants before study.

All included patients were between 18 and 70 years old, were HCV-Ab positive, and had detectable HCV RNA by PCR before treatment. Exclusion criteria included co-infection with HBV or HIV, presence of malignancy, and Child score more than 9.

Enrolled patients were subdivided based on antiviral protocol: SOF/DCV protocol, which combined SOF (400 mg)–DCV (60 mg) oral tablets (n = 340 patients), and SOF/LVD protocol, which combined SOF (400 mg)–LDV (90 mg) oral tablets (n = 90 patients).

Baseline assessment of patients included full history taking and clinical evaluation. The following laboratory data were ordered before therapy: complete blood picture, serum bilirubin, serum albumin, alanine transaminase, prothrombin time, serum creatinine, α-fetoprotein, abdominal ultrasound, HCV-RNA-PCR (quantitative), and HBs-Ag.

Monthly during therapy, serum bilirubin, serum albumin, abdominal ultrasound, and serum creatinine were assessed. Post-treatment tests (at 12 weeks to detect ETR and at 24 weeks to detect SVR after treatment) included HCV-RNA-PCR. All patients were checked at each visit (at weeks 4, 8, 12, and 24) for the potential adverse events by a check-list questions, examinations, and laboratory tests as previously mentioned. Check-list questions included headache, gastric upset, skin rash, and sleep disturbance.

Statistical analysis

Data were statistically described in terms of mean ± SD and frequencies. χ^2-Test was used for univariate analysis. A P value less than 0.05 was considered statistically significant.

Results

During the period of the study between January 2017 and January 2018, the total number of patients enrolled was 430, comprising 340 (79%) males and 90 (21%) females whose, age ranged from 19 to 69 years, with mean age of all patients of 45.34 ± 11.3 years. They were enrolled in two groups: SOF/DCV group, which included 340 patients, and SOF/LDV group, which included 90 patients. Baseline data are summarized in Table 1.

Table 2 shows the different response rates among the two groups: the number of patients with SVR in SOF/DCV was 97.4% (n = 331), with relapse rate of 2.6% (n = 9). In SOF/LDV group, the SVR rate was 97.8% (n = 88), and relapse rate was 2.2% (n = 2). The total numbers of patients with SVR in this study were 419 (97.4%), and those with relapses were 11 (2.5%), with P value of 0.003; this was statistically significant.

Table 3 summarizes different adverse events that occur during the course of therapy. All events were self-limited and symptomatically manageable. None of the adverse events forced the patients to discontinue the treatment. SOF/LDV group showed the highest percentage of adverse events (18.9%), which was statistically significant (P = 0.000). Headache was the most frequent adverse events in all group, which was statistically significant (P = 0.000).

In SOF/DCV group, of 293 (86.2%) patients who did not develop adverse events, 285 (97.3%) patients had SVR, and eight (2.7%) patients relapsed. On the contrary, 47 (13.1%) patients developed adverse events, 46 (97.9%) patients had SVR, and one (2.1%) patient relapsed. In spite of the presence of adverse reaction, SVR among this group was 97.9%, whereas relapses were 2.1%, which was statistically insignificant (P = 0.640) (Table 4).

In SOF/LDV group (90 patients), of 72 (80%) patients who did not develop adverse events, 70 (97.2%) patients had SVR and two (2.8%) patients relapsed. On the contrary, 18 (20%) patients who developed adverse events had SVR. In spite of the presence of adverse reaction, SVR among this group was 100%, which was statistically insignificant (P = 0.638) (Table 4).

Table 5 shows that in SOF/DCV group, of 72 patients who had normal ultrasonographic finding of the liver, 71 (98.6%) patients had SVR, whereas one (1.4%) patient relapsed. One patient with fatty liver relapsed. Of 248 patients who had diffuse liver disease (DLD), 243 (98%) patients had SVR, whereas five (2%) patients relapsed. Of 19 patients who had cirrhotic ultrasonographic finding of the liver, 17 (89.5%) patients had SVR and two (10.5%) patients relapsed.

The total number of relapsed cases in SOF/DCV group was nine cases. Most of them (five cases) had DLD. The highest percentage of SVR was among those who had DLD and normal liver, which was statistically highly significant (P = 0.000). In

Table 1 Basic characteristics of patients

Type of treatment	Total (*n*=430) [*n* (%)]	SOF/LDV (*n*=90) [*n* (%)]	SOF/DCV (*n*=340) [*n* (%)]	*P*
Age	Age range from 19 to 69 years with mean age 45.34±11.3 years			
Sex				0.000*
Male	340 (79)	47 (52.2)	293 (86.2)	
Female	90 (21)	43 (47.8)	47 (13.8)	
Comorbidity				
No	362 (84.1)	75 (83.3)	287 (84.4)	0.092
DM	17 (3.9)	15 (16.6)	2 (0.58)	
Cardiac (HTN-IHD)	34 (7.9)	0 (0)	34 (10)	
Mixed comorbidity	17 (3.9)	0 (0)	17 (5)	
Normal abdominal US	101 (23.4)	29 (32.2)	72 (21.2)	0.025
Fatty liver	33 (7.6)	32 (35.6)	1 (0.3)	
DLD	275 (63.9)	27 (30)	248 (72.9)	
Liver cirrhosis	21 (4.8)	2 (2.2)	19 (5.6)	

DLD, diffuse liver disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; SOF-DCV, Sofosbuvir/Daclatasvir; SOF-LDV, Sofosbuvir/Ledipasvir. *χ^2-test.

Table 2 Type of treatment and type of response in each group

Type of treatment	Type of response [*n* (%)]	
	SVR	Relapse
SOF-DCV (*n*=340)	331 (97.4)	9 (2.6)
SOF-LDV (*n*=90)	88 (97.8)	2 (2.2)
Total (*n*=430)	419 (97.4)	11 (2.5)

P=0.003 (χ^2-test). SOF-DCV, Sofosbuvir/Daclatasvir; SOF-LDV, Sofosbuvir/Ledipasvir; SVR, sustained virologic response.

SOF/LDV group (90 patients), 29 patients had normal ultrasonographic finding of the liver, of which 28 (96.6%) patients had SVR, whereas one (3.4%) patient relapsed.

A total of 32 patients who experienced fatty liver disease had SVR (100%). Of 27 patients who had DLD, 26 (96.3%) patients had SVR, whereas one (3.7%) patient relapsed. Two patients who had cirrhotic ultrasonographic finding of the liver achieved SVR. The total number of relapsed cases in SOF/LDV group was two; one of them had normal liver ultrasonography and the other had DLD. The highest percentage of SVR was among patients with fatty liver, which was statistically insignificant (P = 0.742).

In SOF/DCV group, two patients were diabetic; one of them had SVR (50%) whereas the other (50%) relapsed. Thirty four (100%) patients with cardiac diseases [hypertension (HTN) and ischemic heart disease] had SVR. Of 17 patients having mixed diabetes and cardiac disease, 16 (94.1%) patients had SVR and one (5.9%) patient relapsed (Table 6). The total number of relapsed cases in this group was nine cases; most of them (seven cases) had no comorbid diseases. So, the presence or absence of co-morbid disease had no effect on the response, which was statistically significant (P = 0.000). In SOF/LDV group, 15 (100%) patients with diabetes mellitus had SVR. All relapsed patients had no adverse effects, which was statistically insignificant (P = 0.522) (Table 6).

Discussion

In the present study, we reported an overall SVR rate of 97.4%. The highest SVR was found in SOF/LDV group (97.8%) and 97.4% in SOF/DAC group. In the same context, many studies evaluated the outcome of SOF–plus DCV. One of these recent studies was that of Ahmed *et al.* [6], which included 300 Egyptian patients with chronic HCV genotype 4 infection treated with SOF–plus DCV with or without ribavirin for 12–24 weeks. Of 300 patients, 278 (92.2%) patients achieved SVR.

However, a study at the USA done by Sulkowski *et al.* [5], which included 211 patients who received treatment in the form of SOF –DCV, illustrated that 44 patients were infected with HCV genotype 2 or 3 and 167 had genotype 1. As a result, 91% of patients who were infected with HCV genotype 2 or 3 had SVR 12 weeks after treatment and 164 out of 167 patients with genotype 1 infection (98%) had SVR 12 weeks after treatment. The difference from this study might refer to different genotypes of HCV in the USA.

For patients who received SOF plus LDV, similar results were noted in the recent Egyptian study done by Toson *et al.* [7]. This study included 255 patients who were enrolled from four centers in Egypt. Among treatment-naive patients, SVR rates were 98% for those receiving 12 weeks of LDV/SOF both alone and with ribavirin.

In the study of Mizokami and colleagues, patients were enrolled from 19 clinical Japanese centers. Patients were randomly assigned to receive either LDV (90 mg) and SOF (400 mg) or LDV, SOF, and

Table 3 Distribution of adverse reaction for each type of treatment

	Type of adverse reaction [*n* (%)]					
	No	Headache	Gastric upset	Skin rash	Sleep disturbance	Other
SOF-DCV (*n*=340)	293 (86.2)	28 (8.2)	17 (5)	0 (0)	1 (0.3)	1 (0.3)
SOF-LDV (*n*=90)	73 (81.1)	10 (11.1)	4 (4.4)	0 (0)	1 (1.1)	2 (2.2)
Total (*n*=430)	366 (85.1)	38 (8.8)	21 (4.8)	0 (0)	2 (0.4)	3 (0.6)

SOF-DCV, Sofosbuvir/Daclatasvir; SOF-LDV, Sofosbuvir/Ledipasvir. *P*=0.000.

Table 4 Type of response in relation to adverse events

	Adverse reaction	Type of response [*n* (%)]		*P*
		SVR	Relapse	
SOF-DCV	No (*n*=293)	285 (97.3)	8 (2.7)	0.640
	Yes (*n*=47)	46 (97.9)	1 (2.1)	
SOF-LDV	No (*n*=72)	70 (97.2)	2 (2.8)	0.638
	Yes (*n*=18)	18 (100)	0 (0)	

SOF-DCV, Sofosbuvir/Daclatasvir; SOF-LDV, Sofosbuvir/Ledipasvir.

Table 5 Liver ultrasonographic status and the type of response

	US pretreatment	Type of response [*n* (%)]		*P*
		SVR	Relapse	
SOF-DCV	Normal (*n*=72)	71 (98.6)	1 (1.4)	0.000
	Fatty liver (*n*=1)	0 (0)	1 (100)	
	DLD (*n*=248)	243 (98)	5 (2)	
	Liver cirrhosis (*n*=19)	17 (89.5)	2 (10.5)	
SOF-LDV	Normal (*n*=29)	28 (96.6)	1 (3.4)	0.742
	Fatty liver (*n*=32)	32 (100)	0 (0)	
	DLD (*n*=27)	26 (96.3)	1 (3.7)	
	Liver cirrhosis (*n*=2)	2 (100)	0 (0)	

DLD, diffuse liver disease; SOF-DCV, Sofosbuvir/Daclatasvir; SOF-LDV, Sofosbuvir/Ledipasvir; SVR, sustained virologic response; US, ultrasound.

Table 6 Co-existed comorbid disease and type of response

Type of treatment	Comorbid type	Type of response [*n* (%)]		*P*
		SVR	Relapse	
SOF-DCV	No (*n*=287)	280 (97.6)	7 (2.4)	0.000
	DM (*n*=2)	1 (50)	1 (50)	
	Cardiac (*n*=34) (HTN-IHD)	34 (100)	0 (0)	
	Mixed (*n*=17)	16 (94.1)	1 (5.9)	
SOF-LDV	No (*n*=75)	73 (97.3)	2 (2.7)	0.522
	DM (*n*=15)	15 (100)	0 (0)	

All diabetic patients in SOF/LDV reached SVR. DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; SOF-DCV, Sofosbuvir/Daclatasvir; SOF-LDV, Sofosbuvir/Ledipasvir; SVR, sustained virologic response.

ribavirin. SVR12 was achieved in all patients (83 of 83 treatment naive and 88 of 88 treatment experienced) receiving LDV–SOF.

In our study, adverse events were reported in approximately 14.9% of patients, which were minor events (headache, gastric upset, skin rash, and sleep disturbance). Headache was the most frequent adverse effect in all groups. The highest percentage of adverse effects was observed in SOF/LDV group (18.9%) and followed by SOF/DAC group (13.8%).

Likewise, in other SOF plus DCV studies, Ahmed *et al.* [6] reported the adverse effects in 59 (19.7%) patients [fatigue (9%), headache (4%), and insomnia (2.3%)]. However, in the study of Sulkowski *et al.* [5], the adverse effects were reported in 79.2% of patients and were mainly in the form of fatigue (32.2%).

In addition, in studies that evaluated SOF–plus LDV, Toson *et al.* [7] reported minor adverse effects in 31% of patients such as headache (15%), fatigue (10%), and gastrointestinal tract disturbance (6%). Different results were reported in the study of Mizokami *et al.* [8], who noted the adverse effects in 41.5% of patients (71 of 171 patients), mainly in the form of nasopharyngitis [50 (29.2%) of 171], headache [12 (7.0%) of 171], and malaise [nine (5.3%) of 171].

In our study, of 68 patients presented with comorbid disease in the form of DM, HTN, and ischemic heart disease, only two (2.9%) patients relapsed. This reflected the high efficacy of SOF-based regimen in the presence of comorbid disease. Our results regarding this point were similar to the study done by Gayam *et al.* [9] which included 112 patients with chronic HCV treated with two combinations: SOF and ledipasvir (n = 87 patients) and SOF and velpatasvir (n = 25 patients) for 12 weeks. In SOF/LDV group, of 62 patients presented with comorbid disease in the form of DM and HTN, only four (12.9%) patients relapsed in the course of treatment, whereas among SOF and velpatasvir group, of 25 patients presented with DM and HTN, only one (4%) patient relapsed.

In our study, the highest percentage of SVR was among patients with sonographically cirrhotic changes that were detected in SOF/LDV (100% for each), whereas in patient with DLD, the highest percentage of SVR was detected in SOF/DCV (98%). For patients with fatty liver, the highest percentage of SVR was detected in SOF/LDV (100%).

Another study on SOF/LDV combination done by Shiha and colleagues enrolled 255 patients from four centers in Egypt, and of the nine patients with liver

cirrhosis, eight (89%) patients achieved SVR and one (11%) patient relapsed [10].

Conclusion

The use of the two regimens SOF/DCV and SOF/LDV achieved great success rate for viral eradication with minimal tolerable adverse effects. These regimens of therapy had a great margin of safety with high efficacy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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