Evaluation of efficacy and safety of daclatasvir and sofosbuvir in treatment of chronic hepatitis C infection

Abdel-Ghani Abdel-Hameed Soliman, Mohamed A. A. Ghaliony, Sahar M. Hassany, Shymaa A.-B. Ahmed

Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Shymaa A.-B. Ahmed, MSc, Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assiut University, Assiut, Egypt
Postal Code: 12115;
Tel: +20 106 663 5612;
E-mail: shimaabakr85@gmail.com

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Introduction
The era of direct-acting analogs in the management of chronic hepatitis C virus (HCV) infection stared in 2011, and since then, many agents were approved for management of HCV infection.

Aim
To assess the efficacy and safety of daclatasvir and sofosbuvir in the treatment of chronic hepatitis C infection.

Patients and methods
A prospective study was done at El-Rajhi University Hospital. It included 100 patients (75 patients with chronic HCV infection and 25 patients with HCV-related compensated liver cirrhosis). They received dual therapy (sofosbuvir 400 mg plus daclatasvir 60 mg) for 12 weeks or 24 weeks for patients with chronic hepatitis C and patients with liver cirrhosis, respectively.

Results
Mean age of all patients was 51.48 ± 10.90 years. Overall, 64% were males, 52% were from rural areas, and 56% patients were unemployed. Sustained virological response (SVR) 12 was obtained in 98 (98%) patients included in our study, and only two (2%) patients failed to achieve sustained virological response: one patient had chronic hepatitis but took irregular course of therapy, whereas the other was a cirrhotic patient. It was noticed that 69 (69%) patients had no adverse effects during the course of therapy. Headache was the most frequent event occurred in 17 (17%) patients, comprising seven (9.3%) patients with chronic hepatitis C and 10 (40%) patients with liver cirrhosis.

Conclusion
This regimen of therapy has high success rate for viral eradication with minimal tolerable adverse effects.

Keywords:
chronic hepatitis C infection, daclatasvir, direct-acting antiviral drugs, sofosbuvir, sustained virological response

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Introduction

Hepatitis C virus (HCV) is considered the most common blood-borne infection. Worldwide, up to 130–185 million individuals are chronically infected with HCV. Injection drug use is the most common way for HCV transmission in the developed countries, but in the developing countries, invasive procedures and injection-based therapies are the commonest [1].

Chronic infection with HCV is a major public health problem in Egypt, and unfortunately, Egypt has the highest prevalence worldwide, where HCV antibodies are positive in up to 14.7% of Egyptian population in the 14–59-year age groups [2].

Treatment with pegylated interferon (IFN) and ribavirin (RBV) had been the standard of care for HCV-infected patients for a decade, until the development of several direct-acting antivirals (DAAs). These DAAs have been approved variably in various parts of the world either with RBV, or in combination as multiple oral DAAs with or without RBV [3].

The excellent tolerability and high sustained virological response (SVR) rates with all oral therapy for HCV infection in the clinic could signal the end of the need for IFN as an integral component of the standard of care. This transition would reduce the burden of treatment in all HCV-infected patients and allow more individuals to be treated, including those who are intolerant to IFN or are unresponsive to IFN-based therapy [4].

Aim of the work

The aim is to assess the efficacy and safety of daclatasvir and sofosbuvir in the treatment of chronic hepatitis C infection.

Patients and methods

This prospective study included 100 naive patients (75 patients with chronic HCV infection and 25 patients with HCV-related compensated liver cirrhosis). They received a dual therapy (sofosbuvir 400 mg plus daclatasvir 60 mg) for 12 weeks and 24 weeks for chronic hepatitis C and liver cirrhosis, respectively. This study was conducted at El-Rajhi University Hospital.

(1) Inclusion criteria were as follows:
   (a) HCV RNA positivity.
   (b) Age: 18–75 years.

(2) Exclusion criteria were any of the following:
   (a) Total serum bilirubin more than 3 mg/dl.
   (b) Serum albumin less than 2.8 g/dl.
   (c) International normalized ratio (INR) more than or equal to 1.7.
   (d) Platelets count less than 50.000 mm^3.
   (e) Hepatocellular carcinoma.
   (f) Extrahepatic malignancies.
   (g) Pregnancy.
   (h) Inadequately controlled diabetes mellitus (DM).

(3) All studied patients were subjected to the following:
   (a) History taking

Proper history taking of personal, present, past, and family history, including the route of infection, history of comorbidities (DM, hypertension, ischemic heart disease, and chronic kidney disease), history of schistosomal infection/treatment, invasive investigations, previous surgeries, complications (cirrhosis, liver failure, and liver cancer), and current medications.

(b) Clinical examination

Complete clinical examination included general examination (signs of anemia, jaundice, and bleeding tendency) and abdominal examination for hepatosplenomegaly, signs of portal hypertension, and ascites.

(c) Based on imaging findings and laboratory data, the patients were divided into two groups:
   (i) Those with chronic hepatitis and included 75 patients who received dual therapy for 3 months.
   (ii) Those with liver cirrhosis and included 25 patients who received dual therapy for 6 months.

(d) Laboratory investigations
   (i) Complete blood picture.
   (ii) Liver function includes alanine transaminase, aspartate transaminase, serum albumin, and bilirubin.
   (iii) Prothrombin activity (prothrombin time, prothrombin concentration, and INR).
   (iv) Kidney function tests (serum creatinine and serum urea).
   (v) Random blood sugar.
   (vi) Hemoglobin A1C for patients with DM.
   (vii) Pregnancy test for women in child- bearing period.
   (viii) HCV RNA quantitative assay by PCR before the start of the therapy, at the end of first month of therapy, and 3 months after the end of therapy (3 months for chronic hepatitis and 6 months for those with liver cirrhosis).

(e) Regimens of therapy.

Sofosbuvir 400 mg once daily plus daclatasvir 60 mg once daily for 3 months in patients with chronic HCV infection and for 6 months for those with compensated liver cirrhosis.

The study was approved by the faculty's ethics committee, and permission was obtained from the ethics committee to ensure confidentiality. A background about this study and its reasons were explained to the participants, and the targeted population was encouraged to participate without any undue pressure, and a written consent was taken from each participant.

Statistical analysis

Data were statistically described in terms of mean and SD, median, frequencies, and relative frequencies (%). For nonparametric data, χ^2 test was used. A correlation is a single number that describes the degree of relationship between two variables. The most common type is called the Pearson correlation. A P value less than 0.05 was considered statistically significant.

Results

Based on abdominal ultrasonographic examination, 25 (25%) patients had cirrhotic liver: all of them had splenomegaly, but no one had ascites. Thirty (30%)

patients had normal findings and 45% patients had diffuse hepatic pathology. All patients with liver cirrhosis were Child A classification, and no patients received RBV.

Mean age of all patients was 51.48 ± 10.90 years (49.84 ± 11.21 for those with chronic hepatitis and 56.40 ± 8.37 years for cirrhotic patients). Overall, 64% were males, 52% were from rural areas, and 56% patients were unemployed. All cirrhotic patients and 67% patients from those with chronic hepatitis were accidently discovered to have HCV infection (Table 1).

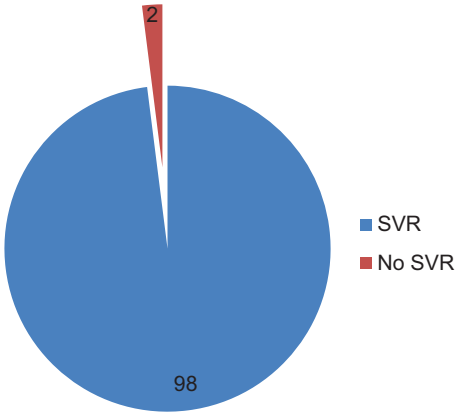
Regarding the demographic data, as shown in Table 1, there was a significant statistical difference between patients with chronic hepatitis and those with liver cirrhosis regarding mean age (P = 0.00). Frequency of DM was more in cirrhotic patients with significant statistical difference (P = 0.00), whereas absence of any comorbidity was more frequent in patients with chronic hepatitis C, with significant statistical difference (P = 0.05). Other comorbidities such as hypertension, ischemic heart diseases, and hypothyroidism had no significant differences between both groups.

Mean complete blood count, kidney function tests, prothrombin concentration, prothrombin time, and INR were within normal range, with the exception of increased liver enzymes of liver function tests. Regarding complete blood picture of both groups, there was only significant statistical difference of mean platelet count with high level in chronic hepatitis C-infected patients (P = 0.00) (Table 2).

There were no significant statistical differences between both groups regarding liver function tests except serum albumin and total protein level, where chronic hepatitis C-infected patients had high significant level than cirrhotic patients (P = 0.04 and 0.03, respectively) (Table 2).

Blood urea and serum creatinine had no significant difference between both groups. Prothrombin

Figure 1



Occurrence of SVR in the studied patients where data were expressed in the form of frequency (%). SVR, sustained virological response.

Table 1 Demographic and clinical data of the studied patients

Variables	All patients (n=100)	Patients with CH (n=75)	Patients with LC (n=25)	P
Age (years) (range, 25-75)	51.48±10.90	49.84±11.21	56.40±8.37	0.00
Sex				0.81
Male	64 (64)	47 (62.7)	17 (68)	
Female	36 (36)	28 (37.3)	8 (32)	
Residence				0.96
Rural	52 (52)	37 (49.3)	15 (60)	
Urban	48 (48)	38 (50.7)	10 (40)	
Occupation				0.59
Unemployed	56 (56)	42 (56)	14 (56)	
Employee	44 (44)	33 (44)	11 (44)	
Comorbidities				
Nothing	81 (81)	65 (86.6)	16 (64)	0.05
Diabetes mellitus	12 (12)	5 (6.7)	7 (28)	0.00
Diabetes mellitus and hypertension	3 (3)	2 (2.7)	1 (4)	0.22
Hypertension	2 (2)	2 (2.7)	0 (0)	
Ischemic heart disease	1 (1)	1 (1.3)	0 (0)	
Hypothyroidism	1 (1)	0 (0)	1 (4)	
Clinical manifestation				0.02
Accidently discovered	92 (92)	67 (89.3)	25 (100)	
Easy fatigability	5 (5)	5 (6.7)	0 (0)	
Diffuse abdominal pain	2 (2)	2 (2.7)	0 (0)	
Boneache	1 (1)	1 (1.3)	0 (0)	

Data were expressed in form of n (%), except for age in the form of mean±SD. CH, chronic hepatitis; LC, liver cirrhosis. P value was considered of significant value if less than 0.05 and compare between patients with chronic hepatitis and those with liver cirrhosis.

Table 2 Baseline laboratory data of all studied patients

Parameters	All patients (*n*=100)	Patients with CH (*n*=75)	Patients with LC (*n*=25)	*P*
Complete blood count				
Hemoglobin (g %)	12.97±0.93	13.1±0.93	12.5±0.81	0.06
Platelets (×10^3/l)	210±74.01	231±76.58	149±57.43	0.00
White blood cells (×10^3/l)	6.14±1.75	6.24±1.79	5.81±1.62	0.09
Liver function tests				
Total bilirubin (mg/dl)	0.89±0.26	0.93±0.25	1.1±0.38	0.22
Direct bilirubin (mg/dl)	0.29±0.03	0.31±0.08	0.32±0.07	0.34
AST (U/l)	89.43±18.93	88.67±17.67	90.72±22.02	0.23
ALT (U/l)	118.40±18.84	112.96±19.43	115.27±20.81	0.19
Serum albumin (g%)	34.35±19.83	35.02±3.31	29.09±1.01	0.03
Total proteins (g%)	85.71±4.91	85.75±4.77	81.01±2.09	0.04
PC (%)	89.89±11.11	95±5.05	84.09±9.07	0.00
PT (s)	11.48±1.32	11.17±1.04	12.40±1.633	0.09
INR	1.01±0.14	0.95±0.072	1.16±0.17	0.51
Kidney function tests				
Creatinine (mg/l)	0.93±0.22	0.94±0.22	0.89±0.21	0.11
Urea (mg/l)	5.67±1.15	5.71±1.18	5.56±1.08	0.94

Data were expressed in form of mean±SD. ALT, alanine transaminase; AST, aspartate transaminase; CH, chronic hepatitis; INR, international normalized ratio; LC, liver cirrhosis; PC, prothrombin concentration; PT, prothrombin time.

Table 3 Adverse effects that developed during the course of therapy

Adverse effects	All patients (*n*=100)	Patients with CH (*n*=75)	Patients with LC (*n*=25)	*P*
Nothing	69 (69)	58 (77.33)	11 (44)	0.00
Headache	17 (17)	7 (9.33)	10 (40)	0.00
Diarrhea	5 (5)	3 (4)	2 (8)	0.01
Abdominal cramps	3 (3)	3 (4)	0 (0)	-
Bloating	3 (3)	2 (2.67)	1 (4)	0.04
Epigastric pain	2 (2)	2 (2.67)	0 (0)	-
Joint pain	1 (1)	0 (0)	1 (4)	-

Data were expressed in form of *n* (%). CH, chronic hepatitis; LC, liver cirrhosis.

concentration was significantly high in chronic hepatitis C-infected patients (P = 0.00) (Table 2).

It was noticed that 69 (69%) patients had no adverse effects during the course of therapy. Headache was the most frequent event occurred in 17 (17%) patients, comprising seven (9.3%) patients with chronic hepatitis C and 10 (40%) patients with liver cirrhosis, with significant difference (P = 0.00) (Table 3). Other adverse effects included diarrhea, abdominal cramps, bloating, epigastric pain, and joint pain, which occurred in five (5%) patients, three (3%) patients, three (2%) patients, two (2%) patients, and one (1%), patient, respectively. Diarrhea and bloating were more frequent in cirrhotic patients compared with those patients with chronic hepatitis C with significant statistical difference. Whatever the adverse effects, no patient had to stop therapy or receive any treatment for these adverse effects.

PCR was ordered for all patients at three times: first time was before therapy, second was after 4 weeks, and the last one was done 12 weeks after the end of therapy. The last one was ordered to show the SVR occurred or not.

SVR12 was obtained in 98 (98%) patients included in our study, and only two (2%) patients failed to achieve SVR: one patient had chronic hepatitis, but took irregular course of therapy, whereas the other was a cirrhotic patient (Fig. 1).

Discussion

There is only one Egyptian study about the use of sofosbuvir and daclatasvir in patients with chronic HCV infection. It was done by Rabab *et al.*[5] and included 102 patients who received sofosbuvir 400 mg plus daclatasvir 60 mg with or without RBV for 12 or 24 weeks according to EASL guidelines [6]. Our study had comparable result to that study.

Moreover, a study was done by Fontaine *et al.*[7] at University Paris Descartes, Liver Department, Cochin Hospital, French Institute of Health and Medical Research UMS20. It included 74 genotype four-infected patients who were given a combination of sofosbuvir 400 mg/day plus daclatasvir 60 mg/day, including 15 patients with RBV 1–1.2 g/day for 12 (n = 11) or 24 weeks (n = 36) [7].

Mean ± SD age of all patients in the current study was 51.48 ± 10.90 years (49.84 ± 11.21 for those with chronic hepatitis and 56.40 ± 8.37 cirrhotic). Overall, 64% were males and 36% were females. This was similar to the study done by Leroy *et al.* [8], where the mean age was 53 years for treatment-naïve patients and 58 years for treatment-experienced patients. Moreover, 58 (58%) males were present in treatment-naïve patients (n = 101) and 32 (63%) in treatment-experienced patients. Nineteen (19%) had cirrhosis among treatment-naive patients (n = 101) and 13 (25%) among treatment-experienced patients (n = 51) [8].

The mean age was 50.45 years in a study done by Rabab *et al.*[5] that included 102 patients, where 13 (12.7%) were treatment experienced, 66 (64.7%) were males, and 34 (33.3%) had cirrhosis. Most of them [61 (59.8%) patients] received sofosbuvir and daclatasvir for 12 weeks, whereas in 31 (30.4%) cirrhotic patients, RBV was added [5].

Most of the reported studies agreed that this regimen had a high degree of safety, and in our study, it was noticed that 69 (69%) patients had no adverse effects during the course of therapy. Headache was the most frequent event occurred in 17 (17%) patients, comprising seven (9.3%) patients with chronic hepatitis C and 10 (40%) patients with liver cirrhosis.

Leroy *et al.*[8] showed that daclatasvir and sofosbuvir combination regimen was well tolerated, with no deaths, treatment-related serious adverse events, or discontinuations owing to adverse events. The most frequent adverse effects (≥5%) were headache (19.7%), fatigue (19.1%), nausea (11.8%), diarrhea (8.6%), insomnia (5.9%), and abdominal pain and arthralgia (both 5.3%) [8].

This is in agreement with Egyptian studies, such as Rabab *et al.* [5], in which, sofosbuvir and daclatasvir also were well tolerated; most adverse events were mild in severity and included fatigue and headache, whereas RBV adverse effects included mainly anemia, and this was managed efficiently with dose reduction [5].

SVR12 was obtained in 98% of patients included in our study, and only two patients failed to achieve SVR: one patient had chronic hepatitis, but took irregular course of therapy, whereas the other was a cirrhotic patient.

Leroy *et al.*[8] reported that 17 (11.2%) had treatment failures, with 16 relapses after treatment and one rebound at the end of treatment. There were no viral breakthroughs in this RBV-free regimen [8].

All patients included in the study of Fontaine *et al.* [7] were followed up where all of them attended their week 4 posttreatment visit with a negative HCV RNA result achieving SVR whereas only 24 (23%) of them reached the date of their week 12 posttreatment visit also with negative HCV RNA achieving SVR12 [7].

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Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Gerlac J, Bour R. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology 2003; 125:80–88.

2 Diego F, Adam J, Dewolfe M, Maria F, Torres, Diana M, *et al.* Spatail pidemiology of HCV infection in Egypt: analyses and implication. Hepatol J 2014; 60:1150–1159.

3 Lok AS. HCV NS5A inhibitors in development. Clin Liver Dis 2013; 17:111–121.

4 Bunchorntavakul C, Reddy K. The efficacy and safety of daclatasvir in the treatment of chronic hepatitis C virus infection. Aliment Pharmacol Ther 2015; 42:258–272.

5 Rabab F, Mohamed H, Aisha E, Razavi H, Waked C, Sarrazin R, *et al.* High SVR in the treatment of chronic HCV genotype 4 patients with Sofosbuvir and Daclatasvir (both generic). Endemic Medicine and Hepatogastroentrology, Kars Al Ainy Viral Hepatitis Center, Cairo Univeristy, Internal Medicine, Ain Shams University, Egypt. EASL-AASLD 2016 Special conference. Paris, France.

6 EASL Recommendations on Treatment of Hepatitis C 2016. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. J Hepatol 2017; 66:153-194..

7 Fontaine H, Hezode C, Zoulim F, Samuel D, Bourlière M, *et al.* LP28: Efficacy of the oral sofosbuvir-based combinations in HCV genotype 4-mono-infected patients from the french observational cohort anrs CO22 hepather. The International Liver Congress™ 2015 – 50th Annual meeting of the European Association for the Study of the Liver, Apr 2015, Vienne, Austria. 62, Supplement 2, pp.S278, 2015, (10.1016/S0168-8278(15)30182-3). (hal-01162770).

8 Leroy V, Dumortier J, Coilly A, Duvoux C, Di Martino V, Radenne S, *et al.* High rates of virological response and major clinical improvement during ofosbuvir and daclatasvir-basedregimens for the treatment of fibrosing holestatic HCV-recurrence afterliver transplantation: the ANRS CO23 UPILT study, Abstract 21 presented at the 65th Annual Meeting of the American Association for theStudy of Liver Diseases, Boston, MA, USA, 016; November 7–11.