

Efficacy of Sofosbuvir plus Daclatasvir in Treatment of Chronic HCV Infection in Egyptian Patients: A Prospective Cohort Study

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Background and study aim: Chronic hepatitis C virus infection is a massive health challenge in Egypt. New DAAs in the past few years have proven to be extremely effective in treatment of HCV infection. The aim of this study was to evaluate the efficacy of a sofosbuvir-based treatment protocol composed of sofosbuvir and daclatasvir with or without the addition of ribavirin in Egyptian patients infected with HCV genotype 4 in Sharkia governorate.

Patients and Methods: One hundred patients were included in the study. Patients were divided into three groups, group I: 48 treatment-naïve non-cirrhotic patients who were assigned to receive dual therapy (Daclatasvir+Sofosbuvir) for a duration of 12 weeks, group II: 32 treatment-naïve cirrhotic patients who were assigned to receive triple therapy (Daclatasvir + Sofosbuvir + Ribavirin) for a duration of 12 weeks, and group III: A control group

composed of 20 chronic HCV patients, not receiving antiviral therapy. Patients were followed up thoroughly by clinical and laboratory evaluation monthly throughout treatment and for 3 months after the end of treatment (EOT). In addition, the virological response for each patient was recorded.

Results: No statistically significant difference was found between both groups that received treatment regarding virological response, since 100% of patients achieved SVR12 rates in both groups.

Conclusion: The combination of Daclatasvir plus Sofosbuvir with or without the addition of ribavirin for a duration of 12 weeks has proven to possess high efficacy in the treatment of cirrhotic and non-cirrhotic naïve Egyptian patients with chronic infection with HCV genotype 4 in Sharkia governorate.

INTRODUCTION

Hepatitis C virus (HCV) infection in Egypt represents a massive challenge facing the country with high prevalence rates within the Egyptian population of different age groups. Genotype 4 (GT4) is the most prevalent genotype in Egypt. It is estimated that 10% of the Egyptian population between 15 and 59 years of age are chronically infected with HCV. Moreover, the rate of infection keeps on with age. This means 8-10 million people are living with viral hepatitis with millions more at risk of infection [1].

Since the production of the first direct-acting antiviral (DAA) agent, great advances have been witnessed in the field of chronic HCV treatment.

Sofosbuvir (an NS5B polymerase inhibitor) is the milestone in almost all of the DAA-based therapeutic regimens. It is a nucleotide analogue that inhibits viral RNA synthesis. Approved by the FDA in 2013 [2], Sofosbuvir (SOF) has shifted the field of chronic HCV treatment into another direction through introducing all-oral regimens that are based on using a combination of 2 or more DAAs, providing the following advantages:

- Pangenotypic activity against all known virus genotypes.
- Higher efficacy compared to the previous interferon (IFN)-based treatment regimens (SVR12 rates >90%).
- Shorter duration of therapy (as short as 8 weeks).

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- Fewer adverse effects.
- Possibility of once daily administration that improved adherence of patients and reduced cases of treatment discontinuation.

Daclatasvir (DCV) is an NS5A inhibitor that exerts its action through two mechanisms. The first is blocking HCV RNA synthesis. The second involves inhibiting viral assembly and release. Approved by the FDA in 2015, DCV has been added to SOF as a combination to treat chronic HCV infection [3].

The aim of this study was to evaluate the efficacy of a protocol composed of (SOF+DCV±RBV) in treating naïve Egyptian patients, either cirrhotic or non-cirrhotic, in Sharkia governorate, Egypt.

PATIENTS AND METHODS

This prospective cohort study was conducted in Tropical Medicine Department, Zagazig University Hospitals, Egypt in the period between March 2017 and February 2018. A total of one hundred patients participated in the study.

Inclusion criteria:

All participants were treatment-naïve Egyptian patients infected with chronic HCV, evidenced by +ve HCV RNA quantitative PCR results with at least twice elevations of liver enzymes in the preceding 6 months. In addition patients without and with compensated cirrhosis were included. Diagnosis of cirrhosis was carried out by means of combined imaging, clinical, and laboratory data.

Exclusion criteria:

Total serum bilirubin >3mg/dl, platelet count <50000/mm³, serum albumin <2.8 gm/dl, INR ≥1.7, HCC and extra hepatic malignancy, patients co-infected with HBV or HIV, co-existence of a metabolic or an autoimmune liver disease, and presence of cerebrovascular disease, coronary artery disease, neoplastic disease, or severe retinopathy.

In addition, patients who are pregnant or women who are not using adequate contraception, inadequately controlled diabetes mellitus (HbA1c > 9%), patients with prior exposure to any IFN, ribavirin (RBV), or other approved or experimental HCV-specific DAAs, age below 18 years, and patients who did not give consent to participate in the study were not included.

Patients were divided based on the latest protocol of the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) [4] and the latest guidelines established by the European Association for the Study of the Liver (EASL) [5] into 3 groups:

- Group I: Forty eight treatment-naïve non-cirrhotic patients who administered dual therapy (DCV + SOF) for a duration of 12 weeks.
- Group II: Thirty two treatment-naïve cirrhotic patients who administered triple therapy (DCV + SOF+RBV) for a duration of 12 weeks.
- Group III: Twenty chronic HCV patients with similar age, gender, and child classification as the treatment groups who were not receiving any treatment for the virus during the study (control group).

SOF and DCV were administered at a dose of 400mg q.d orally and 60mg q.d orally respectively. For those who received RBV, 600 mg were administered daily orally.

The following were carried out for all participants:

- Recording full history.
- Complete general and local examination.
- Investigations including:
 - Laboratory investigations: Complete blood picture (CBC), liver function profile (S. bilirubin, S.albumin, ALT, AST, ALP, and total protein), coagulation profile (PT and INR), kidney function profile (S.creatinine), viral markers (HCV IgG and HBsAg), TSH, blood sugar and HbA1c for diabetics, Alpha-feto protein (α-FP), and HCV PCR for detection of virus RNA.
 - Imaging studies: Abdominal ultrasonography (U/S) for assessment of the liver, detection of ascites, diagnosis of cirrhosis, and exclusion of hepatic focal lesions [6, 7].

Follow up:

Patients were followed up throughout the course of treatment by clinical evaluation, CBC, liver function tests, and kidney function test after one week and two weeks of treatment, then every month till the end of treatment (EOT). PCR for HCV RNA was performed 4 weeks after initiation of therapy, End of Treatment (EOT), and 3 months after cessation of therapy (SVR12).

End points:

The percentage of patients in each treatment group achieving sustained virological response (SVR12) was considered the primary efficacy end point. SVR12 was defined as HCV RNA less than 15 IU/mL when measured twelve weeks after cessation of therapy [5].

Statistical analysis:

Statistical analysis of collected data was carried out using IBM®SPSS program, version 20.

Differences between qualitative variables were examined via Chi square test (χ^2). On the other hand, expression of quantitative data was in terms of mean \pm SD (Standard Deviation) for parametric data, while mean and range were used for non-parametric data.

Parametric variables among the three groups were compared via independent samples t-test. In addition, changes before and after the course of treatment for parametric variables were compared using paired samples t-test. Quantitative data at different time intervals were compared using one way ANOVA test. Significance Level was defined at P-value \leq 0.05 [8].

RESULTS**Study population:**

This study included 100 patients from Sharkia governorate, Egypt with chronic HCV GT4 infection. Patients' age ranged from 27 to 72 years old. Out of the 80 patients in the treatment groups, male represented 40% (32), while female represented 60% (48). 48 patients (60%) were non-cirrhotic and 32 (40%) patients were cirrhotic. All cirrhotic patients were Child A.

No statistically significant difference in demographic data was present at baseline among the three groups included in the study as (Table 1) shows.

Patients in this study were treated according to the latest Egyptian guidelines of the NCCVH [4], which are in accordance with the latest guidelines issued by the WHO [9].

Virological response:

Results of this study show with no doubt the high efficacy of the protocol composed of DCV+SOF for a duration of 12 weeks with or without the addition of RBV in treatment of both non-cirrhotic and cirrhotic patients. This is highly evident by the SVR12 rates achieved in both groups that received treatment, where 100% of patients in both dual and triple therapy groups achieved SVR12. Moreover, the results of PCR tests were negative 4 weeks after initiation of therapy, and continued to be negative at EOT, and 3 months after EOT (SVR12) (Table 2).

Biochemical and clinical parameters:

It seems that biochemical and clinical parameters could benefit from such combination. Statistically significant differences in almost all measured parameters were observed in the data pretreatment and at EOT as shown in (Table3).

Furthermore, statistically significant differences in these parameters were observed since the beginning of treatment and were apparent in the data collected throughout the course of treatment, though not shown here.

Table 1: Comparison of clinico-demographic Findings among different groups

	Treatment groups		Control group Group3
	Group1 (Dual)	Group2 (Triple)	
Age (years)	46.71 (27-72)	50.47 (31-67)	51.50 (27-72)
Gender	Male	13 (40.6%)	8 (40%)
	Female	29 (60.4%)	12 (60%)

Table 2: Comparison of HCV RNA before and after treatment among different groups

PCR Results	Control N=20	Treatment groups	
		Dual N=48	Triple N=32
Baseline PCR	974660.00 (39400-3500000)	1337964.58 (35600-12960300)	2211312.50 (43000-17949800)
PCR M1	-----	Negative	Negative
PCR M3	-----	Negative	Negative
PCR M6	-----	Negative	Negative

Table 3: Changes in laboratory parameters before and after end of treatment in dual and triple therapy groups

Measured Parameters	Group I (Dual therapy) N=48				Group II (Triple therapy) N=32			
	Mean (Pretreatment)	Mean (EOT)	Mean difference \pm SD	P-value	Mean (Pretreatment)	Mean (EOT)	Mean difference \pm SD	P-value
Hemoglobin (11.5-15.5 g/dl)	12.88	13.33	-0.45 \pm 0.83	.000	13.08	13.39	-0.31 \pm 0.69	.016
WBCs (4-11 $10^9/L$)	7.46	6.69	0.77 \pm 1.27	.000	6.51	6.29	0.23 \pm 1.95	0.515
Platelets (150-450 $10^9/L$)	191.94	216.83	-24.89 \pm 46.77	.001	242.97	210.78	32.19 \pm 304.02	0.554
Bilirubin (Up to- 1.2 mg/dl)	0.79	0.52	0.28 \pm 0.3	.000	0.89	0.58	0.31 \pm 0.3	.000
Serum creatinine (0.7- 1.2 mg/dl)	0.89	0.88	0.008 \pm 0.18	0.730	0.83	0.91	-0.08 \pm 0.17	.008
INR (0.8- 1.2)	1.06	0.96	0.09 \pm 0.18	.001	1.12	0.98	0.14 \pm 0.16	.000
ALT (Up to- 40 U/L)	45.06	21.02	24.04 \pm 23.6	.000	44.91	20.41	24.5 \pm 24.53	.000
AST (Up to- 41 U/L)	47.71	20.27	27.44 \pm 23.25	.000	44.63	20.31	24.31 \pm 20.98	.000
Albumin (3.5- 5.2 g/dl)	3.9	4.15	-0.25 \pm 0.32	.000	3.93	4.17	-0.24 \pm 0.27	.000

Note that (-) sign indicates the increase in the mean of a measured parameter at the end of treatment.

DISCUSSION

Unfortunately, Egypt is known for its high prevalence rate of HCV infection in the world as reported by the WHO in 2016 [10]. Based on the data from the Egyptian Health Issue Survey (EHIS) in 2015, it was estimated that approximately 3.7 million persons in Egypt suffer from HCV infection [1].

Following its approval for use in treatment of HCV infection, the high efficacy it achieved along with being known for its pangenotypic activity, has gained SOF the approval to be used in treatment of GT4 infection in Egyptian patients.

Moreover, Egypt was licensed to manufacture certain generic products of the potent DAA,

including sofosbuvir and daclatasvir, making them available at affordable prices [11].

In November 2015, the NCCVH protocol was updated and new regimens were added including SOF+DCV±RBV among other regimens [4]. Since it is the currently applied regimen and since previous studies have recommended further studies with close monitoring and thorough follow up of patients in attempt to assess the efficacy profile of DCV+SOF regimen with or without RBV, SOF+DCV+RBV regimen was the focus of this study.

In this study, the female predominance was obvious, highlighting the high exposure rate and the percentage of adult females seeking medical advice, which may reflect increased awareness in the community regarding HCV treatment with current campaigns of the Ministry of Health and Population (MOHP) for eradication of HCV. These results are in contrast with the reported male predominance by Gad et al. [12] and Mabrouk et al. [13].

In this study, SVR12 rate of 100% was reported, indicating the high efficacy of SOF+DCV regimen. Such results are in agreement with Ahmed et al. [14] who documented the high antiviral potency of the combination of SOF+DCV ± RBV for a duration of 12 weeks, with 94.12% SVR12 rate in treatment-naïve Egyptian patients without or with cirrhosis. However, Ahmed et al., predicted that older age and cirrhosis were predictors of nonresponse to therapy. These findings were not in agreement with our study since both elderly patients (age up to 72 years old) and cirrhotic patients were included, though all patients were class A on Child-Pugh score, and all achieved 100% SVR12 rates.

The results of this study are also in agreement with El Kassas et al. [15] who stated SVR12 rate as high as 98.9% following treatment with SOF+DCV combination.

It is also in agreement with Abdel-Moneim et al. [16] and Omar et al. [17] who both concluded that DCV + SOF + RBV combination was highly effective in treatment of GT4 Egyptian patients, where the first reported SVR12 rates of 95% and 92%. While the second reported SVR12 rates of 95.4% and 94.7% in dual and triple therapy groups respectively. Though the relatively low SVR rates in triple therapy group particularly

may be a result of inclusion of treatment-experienced patients and different classes of cirrhosis.

It is worth noting that SVR12 rate reported in this study, giving that Egyptian patients are predominantly infected with GT4, is higher than that reported for patients infected with other genotypes and treated with the same protocol, where in a study of Sulkowski et al. [18], the SVR12 rates achieved were 98%, 92%, and 89% in GT1, GT2, and GT3 patients respectively. It is worth noting that the highest rates were achieved in GT1a and GT1b patients who showed 98% and 100% SVR12 rates respectively.

On the other hand, Nelson et al. [19] reported SVR12 rate of 90% in 101 GT3-infected patients who were treatment-naïve and received treatment with a combination of DCV+SOF for a duration of 12 weeks. Compared to the findings of this study, it seems that the treatment protocol possesses higher potency in treatment of GT 4 infected patients.

Finally, not only is sofosbuvir + daclatasvir + ribavirin regimen highly potent when it comes to our cohort of GT 4-infected Egyptian patients, as evidenced by the 100% SVR rate, but also it led to improvements in the clinical items and biochemical parameters by the end of therapy.

Moreover, in addition to its high efficacy, being able to produce sofosbuvir and daclatasvir locally means their affordability, which is largely in favor of this combination and a very important factor to consider. Most likely the combination of SOF + DCV will still be present in the Egyptian market and used in treatment of Egyptian patients in the foreseeable future.

In conclusion, the combination of Daclatasvir and Sofosbuvir with or without ribavirin administered for a duration of 12 weeks is highly effective in treatment-naïve Egyptian patients with or without cirrhosis achieving SVR rates of 100%.

Ethical consideration:

Ethical approval was obtained from the IRB (Institutional Review Board) at Faculty of Medicine, Zagazig University, Egypt. All procedures were explained to patients and a written or thumb-printed informed consent was obtained.

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Conflict of interest: None.

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REFERENCES

1. Ministry of Health and Population [Egypt], El-Zanaty and Associates [Egypt], ICF International. Egypt Health Issues Survey 2015. Cairo, Rockville, MD: Ministry of Health and Population, *ICF International*; 2015.
2. Keating, G.M. and Vaidya, A. Sofosbuvir: first global approval. *Drugs* 2014; 74: 273-282.
3. Antonini TM, Coilly A, Rossignol E, Fougerou-Leurent C, Dumortier J, Leroy V, et al. Sofosbuvir-Based Regimens in HIV/HCV Coinfected Patients After Liver Transplantation: Results From the ANRS CO23 CUPILT Study. *Transplantation* 2018; 102: 119-126.
4. National Committee for Control of Viral Hepatitis (NCCVH) Protocol (2015a). <http://www.nccvh.net/doctorsInformationDetails/L5A9E3DX8Rw=>
5. EASL Recommendations on Treatment of Hepatitis C 2016. *Journal of hepatology* 2017; 66: 153-194.
6. Bluth EI, Ultrasound, a practical approach to clinical problems. *Thieme Publishing Group* 2008. ISBN: 3131168323.
7. McGahan J and Goldberg B. Diagnostic ultrasound. *Informa Health Care*. 2008; ISBN: 1420069780.
8. Elliott AC & Woodward WA, Statistical analysis quick reference guidebook: With SPSS examples 2007.
9. World Health Organization. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. July 2018.
10. World Health Organization. Key facts on hepatitis C treatment. Geneva: World Health Organization; 2016. (http://www.who.int/medicines/areas/access/hepCtreat_key_facts/en/).
11. Doss W; Hermez J; Atta H; Jabbour J. Towards a hepatitis-free Egypt: is this achievable? *East Mediterr Health J*. 2018; 24(7):609–610.
12. Gad R, Males S, El-Makhzangy H, Shouman S, Hasan A, Attala M, et al., Predictors of a sustained virological response in patients with genotype 4 chronic hepatitis C. *Liver Int*. 2008, 28(8): 1112-1119.
13. Mabrouk M, El-Raziky M, Zayed N, Salama R, El-Akel W, Awad T et al., Clinical, biochemical and pathological profiles of 5464 Egyptian chronic hepatitis C-infected patients. *Hepatology* 2013; 60(127):1731-1735.
14. Ahmed OA, Elsebaey MA, Fouad MHA, Elashry H, Elshafie AI, Elhadidy AA, et al. Outcomes and predictors of treatment response with sofosbuvir plus daclatasvir with or without ribavirin in Egyptian patients with genotype 4 hepatitis C virus infection. *Infection and Drug Resistance* 2018; 11: 441-445.
15. El Kassas M, Omran D, Elsaed K, Alborai M, Elakel W, El Tahan A, et al. Spur-of-the-Moment Modification in National Treatment Policies Leads to a Surprising HCV Viral Suppression in All Treated Patients: Real-Life Egyptian Experience. *Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research* 2018; 38: 81-85.
16. Abdel-Moneim A, Aboud A, Abdel-Gabaar M, Zanaty MI, Ramadan, M. Efficacy and safety of sofosbuvir plus daclatasvir with or without ribavirin: large real-life results of patients with chronic hepatitis C genotype 4. *Hepatology International* 2018; 12: 348-355.
17. Omar H, El Akel W, Elbaz T, El Kassas M. Generic daclatasvir plus sofosbuvir, with or without ribavirin, in treatment of chronic hepatitis C: real-world results from 18 378 patients in Egypt. 2018; 47: 421-431.
18. Sulkowski MS, Gardiner DF, Rodriguez-Torres, M, Reddy KR, Hassanein T, Jacobson, I., et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *The New England Journal of Medicine* 2014; 370: 211-221.
19. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* (Baltimore, Md.) 2015; 61: 1127-1135.