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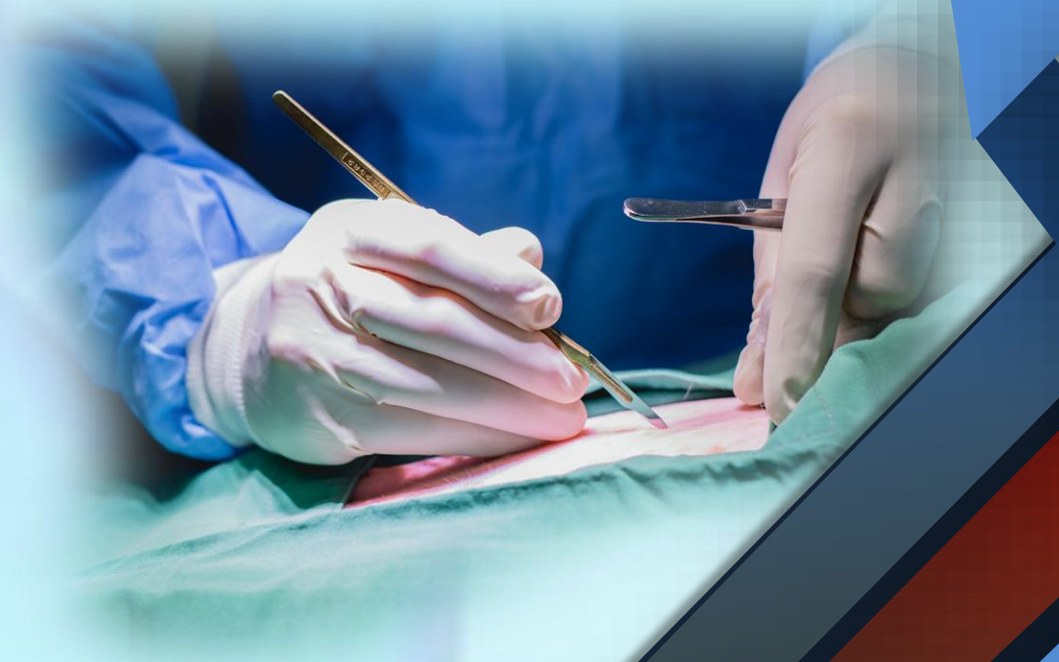

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Original article

Safety and Efficacy of Sofosbuvir and Daclatasvir in The Treatment of Chronic HCV Infection in Elderly Egyptian Patients

Mohamed G. Mohamed; Mohamed B. Bastawy; Mostafa A. Elhawary; Mohamed R. Rashed

Department of Hepatogastroenetrology and Infectious Diseases, Faculty of Medicine, Al-Azhar University, Egypt

Corresponding author: Mohamed G. Mohamed
Email: dr_ghreep90@Azhar.edu.eg

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ABSTRACT

Background: Chronic Hepatitis-C virus [HCV] infection is endemic in Egypt, with the highest prevalence worldwide. There are few studies on the effectiveness and safety of direct acting antivirals in treating geriatric patients with chronic HCV.

Aim of the work: This study aimed to determine the efficacy and safety of sofosbuvir and daclatasvir with or without ribavirin in treating chronic HCV infection in geriatric Egyptian patients.

Patients and Methods: In this study, we analyzed the medical files of 100 patients with chronic HCV, ≥ 65 years old, naïve, and eligible for HCV treatment. Patients were classified into: Group I; 50 patients without cirrhosis and Group II; 50 patients with Cirrhosis. All patients were subjected to history taking, clinical and laboratory evaluation. Electrocardiogram [ECG] and echocardiography were also conducted. Polymerase chain reaction [PCR] for HCV- ribonucleic acid [RNA] was performed and compared between groups at baseline, at the end of treatment, and at 12 weeks later. All patients underwent an abdominal ultrasound and fibrosis-4 [FIB-4] score. Group I was treated with sofosbuvir 400 mg and daclatasvir 60 mg once daily for 12 weeks, while weight-based ribavirin was added in group II.

Results: Overall, 95 patients achieved sustained virological response[SVR]-12, three had failed treatment, and two had relapse. There were no significant differences in treatment success between the groups after treatment completion [HCV RNA was below the detection limit in 49 patients in group I and 48 patients in group II] and 12 weeks later [HCV RNA was below the detection limit in 48 patients in group I and 47 patients in group II], with one patient in group I and two patients in group II had failed treatment. There was also a significant decrease in alanine transaminase [ALT] and aspartate transaminase [AST] in both groups after treatment completion. Some patient symptoms like easy fatigability and dyspepsia have been improved with no significant cardiac changes after therapy.

Conclusions: Sofosbuvir and daclatasvir with or without ribavirin are safe and effective in treating elderly Egyptian patients with chronic HCV infection.

Keywords: Egyptians; Hepatitis-C virus; Sofosbuvir; Daclatasvir; Elderly.

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

About 180 million people worldwide live with chronic hepatitis C virus [HCV], which correlates to a global prevalence of 1.1 percent, and millions more are newly infected each year. HCV is a significant cause of liver-related morbidity and mortality. Seven hundred thousand deaths every year from complications related to chronic HCV infection, including cirrhosis and hepatocellular carcinoma [1].

Egypt had the world's most common HCV prevalence [mainly genotype 4] due to earlier schistosomiasis eradication schemes. It is estimated that HCV prevalence is around 4.5% to 6.7% [1].

Higher rates of HCV infection in older people, rural areas like the Nile Delta, and the lower social classes, up to sixty percent, were registered. In Egypt, the prevalence of HCV antibodies is ten times higher than in the US and Europe [2].

The average age of the population infected with HCV and the number of older patients with more advanced liver disease are growing steadily. In addition, this patient's demographic is expected to grow over the following ten years and will contribute to elevated death rates and resource use, which will have a direct impact on public health and healthcare management worldwide [3].

Virus eradication, identified as viral RNA that is undetectable by highly sensitive methods [lower detection limit of 15 IU / mL], is the main goal of antiviral therapy. If this RNA is still undetectable for 12 weeks of discontinuation of treatment, a sustained virologic response [SVR12] is considered [4].

Although the eradication of HCV by antiviral therapy tends to minimize the risk of liver disease complications [5], elderly patients were considered a difficult-to-treat subgroup, given the higher risk of adverse effects, discontinuations, and mortality. Also, the advanced age has been reported to restrict the use of pegylated interferon [IFN] and ribavirin [RBV] in these subjects as a predictor of non-response to interferon-based therapy, and the concomitant comorbidities like metabolic and cardiovascular disease, along with renal, pulmonary, and hematologic conditions limited the use of pegylated interferon [IFN] and ribavirin [RBV] in these subjects[6].

Now that situation is changing rapidly, interferon-free antiviral regimens with direct-acting antivirals [DAAs] have demonstrated higher effectiveness, improved safety, and shortened treatment duration [7].

Several studies have shown the advantages of treating HCV beyond sustained virologic response [SVR]. Subjects with SVR have shown an enhanced quality of life and efficiency at work, regardless of the nature of the liver disease. Recently, it has been demonstrated that subjects over 65 years of age still benefit substantially after achieving SVR[8].

Furthermore, the number of elderly people with chronic liver disease was very small, and there was not enough proof about the efficacy/safety in them. Thus, there is a need for more prospective studies in elderly patients with hepatic cirrhosis to be performed to determine the safety and effectiveness of HCV treatment in this population[9].

AIM OF THE WORK

This study aimed to determine the efficacy and safety of sofosbuvir and daclatasvir as DAAs with or without ribavirin in the treatment of chronic HCV infection in geriatric Egyptian patients aged 65 years or older.

PATIENTS AND METHODS

This was a retrospective, observational cohort study conducted between Al-Azhar university hospitals and the liver institute of Kafr El-Sheikh and included 100 Egyptian patients with chronic HCV infection. The study was approved by Al-Azhar University ethical committee. Patients were selected from April to November 2017.

Eligible patients were those who had real-time PCR positive HCV RNA, aged 65 years or more, naïve for the treatment of HCV, and suitable for treatment according to the Egyptian National HCV Control Program guidelines.

The goal was to study the effectiveness and safety of sofosbuvir and daclatasvir as a direct-acting antiviral, with or without ribavirin, in the treatment of HCV infection in those geriatric

patients. They were divided into two groups: group I included 50 patients with chronic HCV infection without liver cirrhosis, and group II, included 50 patients with chronic HCV with liver cirrhosis.

All patients were subjected to detailed history taking, comprehensive clinical examination with particular stress on stigmata of chronic liver disease, and laboratory investigations including complete blood count [CBC], serum alanine transaminase [ALT], aspartate transaminase [AST], serum albumin, serum bilirubin, pro-thrombin time and international normalization ratio [INR], Alpha-Fetoprotein [AFP], serum creatinine, fasting blood glucose level and glycated hemoglobin [HbA1c]. Electrocardiogram [ECG] and echocardiography were also conducted to determine the heart rate, rhythm, and cardiac functions of all patients. Real-time polymerase chain reaction [PCR] for HCVRNA was done and compared between the groups at baseline [baseline HCV viral load], at the end of treatment [end treatment response [ETR]], and at 12 weeks after the treatment was stopped [sustained virologic response [SVR12]].

As the standard practice during such treatment, the outcome was categorized as a success [SVR12], failure [any HCV RNA detectable at the end of treatment], or relapse [negative HCV RNA at the end of treatment, but positive after 12 weeks].

All patients were subjected to ultrasound study of the abdomen initially and during follow up to verify the predominant findings of liver cirrhosis [liver texture, portal vein diameter, splenic size, and ascites] and to exclude hepatocellular carcinoma [HCC]. Also, fibrosis-4 [FIB4] score was calculated to assess the level of liver fibrosis [FIB4<1.45=no cirrhosis, between 1.45-3.25=inconclusive and > 3.25 = cirrhosis]. Group I received sofosbuvir 400mg and daclatasvir 60mg once daily without ribavirin as a dual therapy for a period of 12 weeks, while group II had 12 weeks' treatment with sofosbuvir, daclatasvir, and weight-based ribavirin as a triple therapy.

We excluded patients with hepatitis B virus [HBV] co-infection, patients with hepatocellular carcinoma or other extrahepatic malignant tumors, total serum bilirubin greater than 3mg/dl, serum albumin below 2.8 g/dl, international normalization ratio [INR] greater than 1.7, platelet count below 50,000/mm, renal dysfunction with glomerular filtration rate [GFR] below 30ml/minute and non-compliant patients.

Statistical Analysis

Data were analyzed using Statistical Program for Social Science [SPSS] version 18.0. Quantitative data were expressed as mean, plus or minus standard deviation [SD].

Qualitative data were expressed in terms of frequency and percentage.

Statistical analysis was performed using the one-way analysis of variance [ANOVA], Chi-square [X^2] test of significance, and Pearson's correlation coefficient [*r*] test. The Probability [P-value] was considered statistically significant at a value less than 0.05.

RESULTS

This retrospective study included 100 Egyptian patients with chronic HCV. They were classified into two groups; group I: included 50 patients with chronic HCV infection without liver cirrhosis, and group II: included 50 patients with chronic HCV with liver cirrhosis. Of these, 54 [54%] were males, and 46 [46%] were females, with the mean age were 68.5 ± 2.4 in group I and 68.2 ± 3.1 in group II with no statistically significant difference between the two groups [p-value = 0.6] as regard age and sex.

Regarding clinical symptoms and signs in the studied patients before and after treatment, there were significant improvements in easy fatigability, general weakness, abdominal distention, and dyspepsia **[Table 1].** Basic laboratory investigations before and after treatment revealed that there was a highly significant decrease in liver enzymes [ALT and AST] in both groups with decreased RBCs number and hemoglobin levels in group II only. But, there were no significant differences as regards other liver function tests [Total bilirubin serum albumin, and INR], platelets count, alpha-fetoprotein [AFP], serum creatinine in both groups **[Table 2].** Ventricular function [Ejection fraction] and heart rate in both groups before and after treatment revealed non-significant differences **[Table 3].**

In the studied patients, there were no significant differences between both groups as regard cure rates as in group I at the end of therapy, HCV RNA PCR was negative in 49 patients [98%], and in group II it was negative in 48 patients [96%], and after 12 weeks it was negative in 48 patients [96%] and 47 patients [94%] respectively. One patient [2%] had failed treatment in group I and two patients [6%] in group II **[Table 4]**.

Of the 100 patients included in the study, PCR was negative in 97 patients [97%], at the end of therapy [ETR] and in 95 patients [95%] at 12 weeks follow up after completion of treatment, failure of treatment was in 3 patients [3%] and virologic relapse was in 2 patients [2%] in the settings of HCV RNA PCR follow up at the end and 12 weeks from the end of the treatment **[Table 5]**.

Table [1]: Clinical data [symptoms and signs] of all patients before and after therapy

		Before [N [%]]	After [N [%]]	P Value
Symptoms				
Easy fatigability		56 [56%]	27 [27%]	<0.001
General weakness		65 [65%]	31 [31%]	<0.001
Abdominal distension		40 [40%]	34 [34%]	0. 02
Dyspepsia		60 [60%]	42 [42%]	0.03
No compliant		25[25%]	30 [30%]	0.7
Signs				
Bilateral lower limb edema		2 [2%]	2]2%]	0.9
Ascites		0 [0%]	0 [0%]	..
Jaundice		0 [0%]	0 [0%]	..
Heart rate	Normal	93 [93%]	95[95%]	0.2
	Tachycardia	0 [0%]	3[3%]	0.3
	Bradycardia	7 [7%]	2[2%]	0.4
Regular rhythm		100 [100%]	100 [100%]	1

Table [2]: Basic laboratory investigations before and after treatment in group I.

	Group I				Group II			
	Before therapy [n=50]	After therapy [n=50]	*t*-test		Before therapy [n=50]	After therapy [n=50]	*t*-test	
	Mean±SD	Mean±SD	*t*	*p*	Mean±SD	Mean±SD	*t*	*p*
RBCs [millions/ul]	4.2±0.5	4.09±0.3	1.2	0.2	4.1±0.4	3.4±0.3	**8.8**	**<0.001***
Hb [g/dl]	13.6±1.4	13.6±0.6	0.03	0.9	13.3±1.5	10.03±1.07	**12.1**	**<0.001***
WBCs [X 10^3/ ul]	7.8±2.5	8.9±1.7	0.8	0.3	6.1±1.7	6.03±1.4	0.2	0.8
Platelets [X 10^3 /ul]	309.8±35.2	303.7±60.6	0.6	0.5	150.46±56.9	149.9±51.3	0.006	0.9
ALT [TU/L]	61.4±29.4	24.8±6.3	**3.8**	**<0.001***	54.6±30.09	30.4±6.3	**5.5**	**<0.001***
AST[IUL]	62.4±33.4	31.02±3.9	**2.4**	**<0.001***	54.9±29.5	35.2±3.8	**4.6**	**<0.001***
T. Bilirubin [mg/dl]	0.8±0.4	0.7±0.1	2.05	0.5	1.07±0.4	0.9±0.3	0.1	0.7
ALB [g/dl]	4.08±0.3	4.2±0.2	2.3	0.1	3.7±0.5	3.3±0.2	4.2	0.2
INR	1.04±0.07	1.07±0.09	1.6	0.1	1.11±0.1	1.12±0.1	0.6	0.5
AFP [IU/L]	8.4±2.8	8.8±1.5	0.2	0.8	9±2.8	9.3±1.5	0.1	0.8
Creatinine[mg/dl]	0.83±0.23	0.87±0.23	0.8	0.4	0.91±.04	0.8±0.2	0.3	0.6

Table [3]: Ejection fraction [EF%] and heart rate changes in both groups before and after therapy.

		Before therapy [n=50]		After therapy [n=50]		t-test	
		Mean	±SD	Mean	±SD	t	p-value
Group I.	Ejection Fraction [%]	63.6	2.7	64.5	3.5	1.5	0.1
	Heart rate [beat/min]	87	4.4	84	3.9	1.9	0.2
Group II.	Ejection Fraction [%]	62.5	2.9	61.7	2.5	1.4	0.1
	Heart rate [beat/min]	90	4.2	88	3.7	1.9	0.2

Table [4]: Comparison between group I and group II as regard HCV RNA PCR at the end of therapy [ETR] and after 12 weeks [SVR12].

		Group 1 [n=50]	Group 1 [n=50]	P-value
HCV RNA PCR [ETR]	Positive	1 [2%]	2 [4%]	0.3
	Negative	49 [98%]	48 [96%]	
HCV RNA PCR [SVR 12]	Positive	2 [4%]	3 [6%]	0.3
	Negative	48 [96%]	47 [94%]	

Table [5]: HCV RNA PCR of all studied patients before and after therapy.

		HCV-RNA PCR [before therapy] [n=100]	HCV-RNA PCR [at the end of therapy] [n=100]	HCV RNA PCR [after 12weeks] [n=100]	P-value
HCVRNA PCR	Positive	100 [100%]	3 [3%]	5 [5%]	**<0.001**
	Negative	0 [0%]	97 [97%]	95 [95%]	**<0.001**

DISCUSSION

There was a lack of evidence in the current literature to prove the effectiveness and safety of the new DAAs in treating HCV infection in the elderly due to the small number of subjects aged 65 years or more included in the studies evaluating DAAs efficacy[10]. Patients 65 years or older also get substantial advantages in patient performance and quality of life after attaining SVR[8].

Results of our study revealed that red cell count and hemoglobin level were significantly decreased in group II after treatment when compared to values before treatment. Similar results were obtained regarding liver enzymes [ALT, AST] and PCR virus load in both groups. After treatment by 12 weeks, the SVR is still comparable to values at the end of treatment. Only two patients had increased viral load again [relapse]. Cardiac functions and other lab investigations did not change significantly at the end of treatment. These data reflected the efficacy and safety of both treatment regimens.

These results are comparable to **Cnoti et al.[10],** who showed in his study on 282 patients with chronic HCV aged 65 years or older receiving DAAs that SVR was reached in 94.7% and in 1.4% of patients, antiviral therapy was stopped prematurely at eight weeks due to adverse effects. Failure of treatment was 3.9%. However, this cohort was different from ours in terms of genotypes and treatment regimens. Current results are also in line with **Mohamed et al. [11],** who studied the effect of sofosbuvir and daclatasvir with ribavirin on parameters of liver function and clinical outcome in Egyptian patients with chronic HCV infection. SVR was achieved in 357 patients [98.3%] out of the 363 patients involved, while four patients [1.1%] showed the failure of treatment, and two patients [0.5%] died during the study. No mortality was reported in the current study.

Vermehren et al.[12] conducted a study on DAAs effectiveness in the treatment of 541 elderly patients with HCV, and found that SVR was similar to our results with a rate of 98% and 91% in patients aged 65 years or more and patients less than 65 years old, respectively, however in their study, they studied the drug-drug interaction in people with chronic HCV which not addressed in the current study due to difficulties in patients follow up.

In our study, none of the patients stopped treatment due to side effects of the used medications either in cirrhotic or in non-cirrhotic patients. This finding agreed with **Sherigar et al.[13],** who found that none of the patients terminated the treatment regimen due to side effects.

The findings of the current work are consistent with **Mohamed et al.[11],** who reported a significant improvement in liver function tests and clinical outcome in successfully eradicated HCV patients by DAAs, sofosbuvir, and daclatasvir plus ribavirin as liver transaminases ALT and AST showed significant improvement from [63.2±27.6 and 58.1±19.1 U/l, respectively] at baseline to [27.6±

18.3 and 31.4 ± 23.4, respectively]. It was in total agreement with our results as liver transaminases ALT and AST showed improvement in group I from [61.4 ± 29.4 and 62.4 ± 33.4 U/l,] at baseline to [24.8 ± 6.3 and 31.02 ± 3.9,] and in group II from [54.6 ± 30.09 and 54.9 ± 29.5 U/l,] at baseline to [30.4 ± 6.3 and 35.2 ± 3.8].

However, the same authors [Mohamed et al.[11]] showed significant improvement in serum bilirubin levels, which reduced significantly from 1.43 ± 0.67 mg/dl before treatment to 1.02 ± 0.37 mg/dl after treatment. Similarly, they reported a significant reduction of INR, a significant increase of serum albumin, and mean platelet count after treatment when compared to baseline values. However, the serum hemoglobin was reduced from 11.67 ± 1.51 to 11.27 ± 1.58mg/dl after 12 weeks of completion of treatment. This is compatible with that occurred only in group II of the current work. This reduction of hemoglobin could be attributed to ribavirin therapy.

The differences between our results and that of **Mohamed et al.[11]** regarding liver functions and platelet count may be explained by the lack of variability in the chronically affected liver status in our study as most of the included patients were compensated. On the other hand, **Mohamed et al.[11]** included variable patients as regard Child classification and associated co-morbidities.

Results of cardiac function in the current study are in line with **Sulkowski et al.[14]** who reported that symptomatic bradycardia and dysrhythmias had not previously been linked with sofosbuvir without amiodarone and another directly acting antiviral therapy.

Overall results of the present study are comparable with **Conti et al.[10]** and **Vermehren et al.[12],** who stated that, in the current literature, the limited studies about safety and efficacy of DAAs in HCV treatment in the elderly have shown that treatment is safe and effective with careful evaluation of the patients before starting and strictly follow up during treatment and with dose adjustment, unwanted adverse reactions and drug-drug interaction could be prevented.

The retrospective nature of our research with the incomplete documentation of all drug-related adverse effects and lack of strict patient follow up may be a limitation of the results of this study.

In conclusion, sofosbuvir and daclatasvir, with or without ribavirin, have been successful and safe in the treatment of chronic Hepatitis-C infection in elderly Egyptian patients, and patients' age does not have a major impact on the success rate or incidence of adverse effects compared to those recorded in younger people. In geriatric patients, liver cirrhosis doesn't have a major effect on the SVR. More studies are needed to evaluate the newer DAAs regimens in elderly patients.

Financial and Non-Financial Relationships and Activities of Interest

There is no conflict of interest or financial disclosures related to this work.

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