Safety and Efficacy of Direct-Acting Antivirals for Treatment of Chronic Hepatitis C in Population Aged 60 Years and Older in Upper Egypt

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Abstract

Background: Egypt is the country of highest prevalence of chronic HCV infection. Elderly infected individuals are more liable than younger infected individuals to have increased course of infection, increased risk of disease progression, and consequently increased incidence of occurrence of advanced liver disease.

Objectives: The current study aimed to assess the safety and the efficacy of the treatment with direct acting antivirals based regimens in hepatitis C virus infected individuals aged ≥60 years.

Patients and methods: three hundred elderly individuals with chronic hepatitis C virus infection recurred from Unit of Hepatic Viruses Treatment, Qena university hospital, South Valley University, Qena, Egypt. Child–Pugh grade A, were involved in this study, treated with DAAs for twelve weeks, either dual therapy or triple therapy(with addition of ribavirin), according to criteria of the national committee for chronic viral hepatitis.

Results: The Overall CHC infected individuals mean ages were 69.9 ± 5.3 years, 71.7% were male and 18.3% were females. The sustained virological response (SVR) rate at 12 weeks post-treatment was 96% (288/300). There were statistically significant correlations between virological failure and degree of fibrosis, rates of sustained virological response were 98.8% in patients with no liver cirrhosis and 84.5 % in patients with established liver cirrhosis, there was statistically significant difference as regard the rate of virological response between patients with and without cirrhosis ($P < 0.001$).

Conclusion: DAAs treatment achieved 12weeks-sustained virological response in 96% of patients with chronic hepatitis C virus-infection with high safety profile. Liver Cirrhosis has negative impact on 12weeks-SVR.

Keywords: Direct-acting anti-virus, SVR, HCV

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Introduction

Chronic hepatitis C virus infection (CHC) is a leading cause of terminal-stage liver disease, development of hepatocellular carcinoma and liver related death worldwide **(Westbrook, 2014).**Worldwide epidemiology of hepatitis c virus infection reveals that the seroprevalence of Anti-hepatitis C virus antibody has raised over the last few decades from 2.3% to 2.8%, correlating about 185 million infections globally **(MohdHanafiah et al., 2013).**

Traditionally, age has been a main limitation of IFN/Ribavirin-based antiviral treatment since it is usually burdened with several treatment- associated adverse effects, specially anemia which may critically deteriorates patient safety, especially among elderly patients with established cardiovascular co morbidities **(Mücke et al., 2019).**

The launching of direct acting antivirals has since revolutionized the hepatitis C virus treatment landscape. Sustained virological response rates for direct acting antivirals therapy exceed 90% in registration trials and are more tolerated than IFN-based treatment **(Kohli et al., 2014)**. Elderly population, particularly those 75 years of age and older, have been precluded from majority of clinical trials and the safety and efficacy of direct acting antivirals have not been precisely evaluated in this special population except for small clinical trial (**Fujii et al., 2017).**I

n general, few real-world data are attainable on direct acting antivirals treatment in old and very old patients. Thus, data on effectiveness and safety of direct acting antivirals in these groups are required. The goal of our study was to assess the safety and the efficacy of the treatment with direct acting antivirals based regimens in hepatitis C virus infected individuals aged ≥60 years.

Patients and methods

This was a prospective study involved 300 chronic hepatitis C virus-infected Egyptian elderly patients.

Setting: Unit of Hepatic Viruses Treatment, Qena University Hospital, South Valley University, Qena, Egypt

The inclusion criteria were: Individuals aged 60 years and older with hepatitis C virus-RNA positivity. The diagnosis of chronic hepatitis C was based on clinical and laboratory data, involving (Positive anti hepatitis C virus antibody and hepatitis C virus PCR (more than 50 IU/ml).

The exclusion criteria constituted HCV-infected patients with decompensated liver cirrhosis (Child grade B and C), patients with ascites, hepatic encephalopathy, pregnant women, patients with established hepatocellular carcinoma, patients with hepatitis B virus or human immunodeficiency virus co-infection, patients with chronic renal impairment (GFR less than 30 ml/minute), patients with INR >1.7, patients with serum albumin <2.8 g/dl, patients with serum total bilirubin >3 mg/dl or platelet count less than 50(10^9/L).

All patients enrolled in the study were subjected to clinical evaluation, laboratory tests, and abdominal ultrasonography to evaluate hepatic echo-pattern of the liver, the patency of the portal vein, and presence of splenomegaly and to rule out presence of hepatocellular carcinoma.

All the patients enrolled in the study were subjected to the following tests:

1) Complete blood count using cell dyne-1800

2) Liver functions test and kidney functions test, assessment for serum alanine aminotransferase enzyme and serum aspartate aminotransferase enzyme (ALT, 0-41 U/L, and AST, 0-38 U/L, serum albumin level, serum total bilirubin, and serum creatinine level (0.50-1.2 mg/dl); using Cobas c311,assessment of prothrombin time (PT), prothrombin concentration (PC) using STA compact Max Coagulation system

3) Hepatitis markers for hepatitis B infection and hepatitis C infection were examined by an enzyme immunoassay (EIA) Cobas e411

4) Hepatitis C virus RNA viral load evaluation by quantitative real-time polymerase chain reaction (QT-PCR) test, using the CobasAmplicor, TaqMan HCV test version 2.0 (the lower detection limit was 15 IU/ml).

Treatment regimen

Patients submitted to direct acting antivirals therapy, depending on the guidelines of the European Association for Study of Liver(**EASL, 2016**). Patients were being monitored at outpatient clinic of department of tropical medicine and gastroenterology, Qena university hospital. 162patients received treatment for twelve weeks with once-daily dose combination treatment of Sofosbuvir (400mg) and Daclatasvir(60mg)and 138 patients received triple combination therapy of Sofosbuvir, Daclatasvir, with addition of Ribavirin.

Monitoring of efficacy and safety

Virological assessment of hepatitis C virus-RNA level was done three times: at the baseline (before beginning of the treatment), at the end of the treatment (EOT) (week 12), and twelve weeks after the end of treatment. The primary efficacy endpoint was established by a sustained virological response at twelve weeks after the end of therapy. Sustained virological response was considered when hepatitis C virus RNA is less than the lower limit of detection (LLOD) at week 12 after end of treatment (sustained virological response-12) by quantitative hepatitis C virus-PCR whereas treatment failure was established as confirmed hepatitis C virus-RNA above the lower limit of detection twelve weeks after end of treatment.

Safety endpoints involved no significant side events, no serious changes in complete blood count test, serum alanine aminotransferase enzyme or kidney functions tests, no discontinuations of treatment due to side effects, or deaths.

The study protocol was approved by Ethical Committee of Faculty of medicine, South Valley University and written informed consent was taken from each patient.

Statistical analysis

Data were studied utilizing a Statistical Program for Social Science (SPSS) version 18.0. Quantitative data were evinced as mean ± standard deviation (M±SD) while qualitative data were evinced as frequency and percentage No(%).Chi-square test: was utilized in comparison of non-parametric data. A one-way analysis of variance (ANOVA), utilized in comparison of more than two means. P-values were established statistically significant at $P < 0.05$.

Results

Baseline characteristics

Three hundred chronic hepatitis C virus-infected patients with their mean ages were (69.9 ± 5.3 years). Patients treated for twelve weeks with direct acting antivirals either with double therapy (54%) or with triple therapy (46%). 215 of these patients (71.7%) were men (males), 40(13.33%) were diabetic patients and 10 (3.3%) were hypertensive patients. The mean body mass index was 27.17 and the number of smokers was 70 patients (23.3%) (Table1). The mean hepatitis C virus-RNA viral load level was 1.064×10^6. (SD±2097724.6)

Depending on Ultrasonographic assessment findings, 58 (19.3%) patients were cirrhotic patients, 131 (43.7%) patients presented with diffuse hepatic pathology and 111 (37%) were presented by normal liver echo pattern. Regarding laboratory tests, the mean values of liver function tests, ALT , AST, AFP, serum total bilirubin, platelet count , INR and serum albumin levels were 37.7 U/L , 35.4 U/L ,7.5 ng/ml ,0.8 mg/ml, 199.1 (10^9/L), 1.1 and 3.9 g/ml respectively (Table 2).

Efficacy

The findings of our study revealed that the sustained virological response was 96% (288/300) of overall patients (Table 4). We found a statistically significant variation between patients who responded to treatment and patients who did not respond to treatment as regard liver cirrhosis. Table (5) reveals highly statistical significant variation (p-value < 0.001) between cirrhotic patients and non-cirrhotic patients as regard sustained virological response. In patients with established liver cirrhosis (n = 58), there were 49 responder to treatment (84.5%) and 9 non-responder (15.5%) while in patients without liver cirrhosis (n = 242), there were 239 responder to treatment (98.8%) and 3 non-responder (1.2%).

Safety

When it comes to Safety and tolerability of direct acting antivirals in old aged patient, no serious side effects were reported during the present study and no-one stop treatment due to adverse events. No important changes happened during or at the end of treatment related to platelet counts, serum alanine aminotransferase levels, or serum creatinine levels between pre-treatment and 4-weaks, 8-weaks and 12-weaks (P>0.05, for all). We found statistical considerable variations in hemoglobin level between pre-treatment and 4-weaks, 8-weaks and 12-weaks (P<0.001, for all). In majority of these cases, anemia was owing to Ribavirin utilized in combination with direct acting antivirals.

Table 1. Description of demographic data in all patients enrolled in the study

Variables		**Studied patients (N = 300)**	
Age(years)	Mean ±SD	69.9 ± 5.3	
Sex	Male	215	71.7%
	Female	85	28.3%
BMI(kg/m²)	Mean ±SD	27.6 ± 5.2	
Regimen	SD	162	54%
	SDR	138	46%
Smoking	Smoker	70	23.3%
Chronic disease	DM	40	13.3%
	HTN	10	3.3%

This table reveals the description of demographic data in all individuals involved in the study. As concerns of age, the mean age of all individuals involved in the study was 69.9 ± 5.3 years with minimum age of 60 years and maximum age of 83 years. As concerns of sex, there were 215 males (71.7%) and 85 females (28.3%) in all individuals involved in the study. As concerns of BMI, the mean BMI of all individuals enrolled in the study was 27.6 ± 5.2 kg/m² with minimum BMI of 15 kg/m² and maximum BMI of 47.5 kg/m². As concerns of regimen, there were 162 individuals (54%) administrated SD regimen and 138 individuals (46%) received SDR regimen in all studied individuals. As concerns of smoking, there were 70 individuals who are smokers (23.3%) and 230 individuals who are non-smokers (76.7%) in all studied individuals enrolled in the study.

As concerns of chronic diseases, there were 40 diabetic individuals (13.3%), 10 hypertensive individuals (3.3%) in all studied individuals enrolled in the study whereas the

remaining 250 individuals had no chronic diseases.

Table 2. Description of laboratory data in all patients enrolled in the study

(N = 300)	Min.	Max.	Mean	±SD
Viral load	78	17231000	1064763.9	2097724.6
ALT	3	169	37.7	26.3
AST	5	193	35.4	23.8
AFP	1	210	7.5	16.7
Bilir.	0.2	2.4	0.8	0.4
PLTs	50	459	199.1	62.9
WBCs	2.1	62	6.1	3.8
Hb	9.8	139	14.1	7.5
Creat.	0.4	1.5	0.9	0.2
ALB	2.8	5.5	3.9	0.5
FBS	7.6	350	106.8	40.7
INR	1	1.6	1.1	0.1

This table reveals the description of laboratory data in all patients enrolled in the study.

Table 3.Description of Sonographic findings in all studied patients.

Variables		Studied patients (N = 300)	
Liver	Normal echopattern	111	37%
	Diffuse hepatic pathology	131	43.7%
	L.C	58	19.3%
Spleen	Normal	283	94.3%
	Splenomegaly	17	5.7%
Portal vein	Patent	300	100%
	Not patent	0	0%

This table reveals the description of findings detected by ultrasonography in all patients enrolled in the study. As concerns of liver, it was normal hepatic echopattern in 111 individuals (37%), diffuse hepatic pathology in 131 individuals (43.7%) and liver cirrhosis in 58 individuals (19.3%). As concerns of spleen, it was normal in 283 individuals (94.3%) and splenomegaly in 17 individuals (5.7%). As concerns of portal vein patency, it was patent in all studied patient (100%).

Table 4. Description of sustained virological response in all patients enrolled in the study

Variables		Studied patients (N = 300)	
SVR	**Responder**	**288**	**96%**
	Non-responder	**12**	**4%**

This table shows the SVR rate (96%) in all studied patients. There were 288 patients (96%) responder and 12 patients (4%) non-responder in the studied patients.

Table 5. Comparison of sustained virological response as regard Liver U/S.

		Liver U/S				P-value
		Cirrhotic (n = 58)		Non-cirrhotic (n = 242)		
SVR	**Responder**	**49**	**84.5 %**	**239**	**98.8 %**	**< 0.001 HS**
	Non-Responder	**9**	**15.5 %**	**3**	**1.2 %**	

This table shows highly statistical significant difference **(p-value < 0.001)** between cirrhotic patients and non-cirrhotic patients as regard SVR rate.

Table 6. Comparison between the baseline results and 4 weeks lab follow up

Variables		Lab Follow up		MW	P-value
		Baseline (n = 300)	4 weeks (n = 300)		
ALT (U/L)	Mean ±SD	37.7 ± 26.3	37.8 ± 25.8	44607.5	0.853 NS
	Median	34	34		
PLTs (x10³/ul)	Mean ±SD	199.1 ± 62.9	201.9 ± 121.4	43797.5	0.571 NS
	Median	193	190		
WBCs (x10³/ul)	Mean ±SD	6.06 ± 3.8	6.03 ± 3.8	44568.5	0.839 NS
	Median	5.6	5.6		
Hb (g/dl)	Mean ±SD	14.1 ± 7.5	12.9 ± 2.02	34064.5	< 0.001 HS
	Median	13.9	12.6		
Creat (mg/dl)	Mean	0.9	0.92	T = 1.2	0.221 NS
	±SD	0.1	0.1		

This table shows no statistical significant difference **(p-value > 0.05)** between baseline and 4 weeks as regard ALT, PLTs, WBCs &Creatinine, and highly statistical significant difference **(p-value < 0.001)** between baseline and 4 weeks as regard Hb.

Table 7. Comparison between baseline and 12 weeks lab follow up

Variables		Lab Follow up		MW	P-value
		Baseline (n = 300)	12 weeks (n = 300)		
ALT (U/L)	Mean ±SD	37.7 ± 26.3	37.6 ± 26.01	44847.5	0.999 NS
	Median	34	33		
PLTs (x10³/ul)	Mean ±SD	199.1 ± 62.9	199.5 ± 63.4	44784.0	0.975 NS
	Median	193	192.5		
WBCs (x10³/ul)	Mean ±SD	6.06 ± 3.8	6.02 ± 3.8	44262.0	0.781 NS
	Median	5.6	5.6		
Hb (g/dl)	Mean ±SD	14.1 ± 7.5	12.7 ± 2.03	32349.0	< 0.001 HS
	Median	13.9	12.6		
Creat (mg/dl)	Mean	0.9	0.92	T = 0.77	0.438 NS
	±SD	0.1	0.2		

This table shows no statistical significant difference **(p-value > 0.05)** between baseline and 12 weeks as regard ALT, PLTs, WBCs &Creatinine, and highly statistical significant difference **(p-value < 0.001)** between baseline and 12 weeks as regard Hb.

Discussion

Chronic hepatitis C infection is a main causative of chronic liver disease, development of liver cirrhosis and hepatocellular carcinoma(**Hessel et al., 2016).** The launch of the direct acting antiviral agents in the treatment of hepatitis C virus infections has revolutionized this domain. Direct acting antivirals treatment presently means that most of infected patients can be

successfully cured with evermore decreasing durations of well tolerated regimens **(Hathorn and Elsharkawy, 2016).**

The findings of our study revealed that the sustained virological response was achieved in 96% (288/300) Overall patients. The results of this study were supported by **Ozono et al**. In which 246 Japanese hepatitis C virus-infected patients aged ≥ 75 years received Sofosbuvir/Ledipasvir. Patients received twelve weeks of therapy with a fixed-dose combination tablet contained 90 mg of Ledipasvir and 400 mg of Sofosbuvir, takenper oral once daily. The median age was 69 years old (range, 29-88 years), and 79 (32%) infected patients were aged ≥ 75 years. The rates of sustained virological response-12 were 99.2%, 99.4%, and 98.7% in the entire population.

Conti et al.demonstrated the efficacy and safety of direct acting antivirals therapy in elderly individuals. In their study, a total of 556 hepatitis C virus-infected patients with established advanced liver disease received interferon-free regimens. 282 (50.7%) infected patients were ≥65 years old and 274 (49.3%) patients were <65 years old. The sustained virological response -12 rate was approximately 92.6%in the overall population.

The current data reported an original finding about the relation between liver cirrhosis and occurrence of virologic failure after 12 weeks of the end of treatment. Rates of sustained virological response were 98.8% in patients without liver cirrhosis and 84.5 % in cirrhotic patients, there were high significant variation between cirrhotic and non-cirrhotic patients **(P < 0.001).**

The results of our study were also supported by **ALLY-3 phase III** study, and **Nelson et al,.(2015)** in which 100 patient who never received HCV treatment before and 51 treatment-experienced patients infected by HCV genotype 3. Patients were submitted to receive open-label daclatasvir 60 mg + sofosbuvir 400 mg orally once daily for twelve weeks. Sustained virological resoponse-12 rates were higher in patients without liver cirrhosis (96%) than in patients with established liver cirrhosis (63 %;) ***(*Nelson et al., 2015*).***

An open-label non-interventional study achieved by **Shiha et al.** that assessed the effect of twelve week of daily orally administrated Sofosbuvirin association with Daclatasvir with or without the addition of ribavirin. Among 1168 patients, the sustained virological response-12 (SVR12) was reached in 96.6% (95% CI 95.1–98.2%) of the patients taking twelve weeks of Daclatasvir/ Sofosbuvir treatment, in 95.7% (95% CI 93.6–97.8%) of the patients taking twelve weeks of Daclatasvir/ Sofosbuvir/ ribavirin. Sustained virological response-12 rate was considerably higher in patients with no liver cirrhosis receiving Daclatasvir/ Sofosbuvironly for twelve weeks (97.4) than in patients with liver cirrhosis (91.7) **(Shiha et al., 2018).**

Direct acting antivirals regimens were typically well tolerated, with no serious adverse effects and no discontinuation of the treatment due to important adverse events. Anemia was frequent in patients received ribavirinin combination with direct acting antivirals. Therefore, elderly patients receiving ribavirin must be carefully monitored for the development of anemia. **Saab et al.** studied the data from four open-label phase three clinical trials that assessed the safety Direct acting antivirals therapy in elderly individuals and concluded that Direct acting antivirals based regimens were safe, and well tolerated in hepatitis C virus-infected patients older than 65 years of age.

Conclusion

Direct acting antivirals based regimens were highly effective with high virological response and high safety profile in elderly hepatitis C virus-infected patients. Liver Cirrhosis has

negative impact on 12weeks-sustained virological response.

Conflict of Interest

The authors of the study have no conflict of interest related to this publication.

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