Hassan *et al. Egyptian Liver Journal* (2023) 13:49
https://doi.org/10.1186/s43066-023-00284-6

Egyptian Liver Journal

ORIGINAL RESEARCH ARTICLE

Open Access

Assessment of hepatic fibrosis, portal hemodynamic changes, and disease severity in patients with HCV-related liver cirrhosis after sustained virologic response to direct-acting antiviral drugs (DAAs)

Waleed Attia Hassan[1*], Sherif I. Kamel[1], Ibrahim Abdel Naby Mahmoud[1], Nahed Makhlouf[1], Mahmoud Moubark[2] and Sahar M. Hassany[1]

Abstract

Background Regression of fibrosis and improvement of portal hemodynamics after achievement of sustained viral response (SVR) in patients with chronic hepatitis C (HCV) is a subject of debate in different studies. Some studies reported improvement in the degree of fibrosis, while others did not find significant changes.

Objective We aimed to evaluate changes in liver fibrosis, portal hemodynamics and clinical outcomes in patients with chronic HCV-related liver cirrhosis after the achievement of SVR with direct-acting antiviral drugs (DAAs).

Patients and methods In our prospective longitudinal study, a total of 100 patients with chronic HCV infection-related liver cirrhosis were recruited, received DAAs, and completed the follow-up period. Clinical evaluation for assessment of liver disease severity using MELD and Child–Pugh class and scores were done. A noninvasive assessment of liver fibrosis using serum biomarkers (APRI index & FIB4 score) and share wave elastography (SWE) was done. Portal hemodynamic evaluation using Doppler ultrasound was done. All were done at baseline and 3 and 12 months after the end of therapy.

Results A significant reduction in the degree of fibrosis was observed. Share wave elastography (SWE) readings showed 19.79% and 30.45% reduction 3 and 12 months after the end of therapy respectively ($P < 0.001$). Regarding the FIB4 score, the percentage of score reduction was 19.8% and 26.46% 3 and 12 months after the end of therapy, respectively ($P < 0.01$). APRI scores showed 22.6% and 41.09% reduction 3 and 12 months after the end of therapy respectively ($P < 0.001$). Significant improvement in Child–Pugh scores 3 and 12 months after the end of treatment was observed. Doppler ultrasound showed a significant increase in portal vein flow velocity, a significant decrease in time average mean velocity, and cross-section area 12 months after the end of treatment.

Conclusion There was a considerable degree of reduction of liver fibrosis, improvement of portal hemodynamics, and Child–Pugh score in cirrhotic HCV patients who achieved SVR after DAAs.

Trial registration ClinicalTrials.gov, ID: NCT03241823. Registered on 08 May 2017.

Keywords Hepatic, Fibrosis, Cirrhosis, Doppler, SVR, SWE

*Correspondence:
Waleed Attia Hassan
wallo403a@aun.edu.eg
Full list of author information is available at the end of the article

Introduction

Before the introduction of direct-acting antiviral drugs (DAAs), there were about 71 million infected patients with hepatitis C virus (HCV) worldwide; of them, 55–85% have had chronic liver disease [1]. It was found that liver cirrhosis complicates 10–30% of patients within 2 decades of infection. Hepatocellular carcinoma was found to develop each year in 1–4% of patients with HCV-related liver cirrhosis [2, 3]. Since 2014, after DAAs' introduction into the clinical practice, there has been a dramatic improvement in HCV management with a shorter duration of treatment and less adverse effects than interferon-based therapy, with SVR reaching 95% of cases [4]. DAAs (in contrast to interferon-based regimens) can be given to patients with liver cirrhosis.

Despite the recent advances in DAAs, data about its effects on the degree of fibrosis regression is still not enough. Reduction of liver fibrosis scores with its clinical impact on the clinical status of the patients is the optimum aim and hope of treatment with DAAs now [5, 6]. Previous studies noted a reduction in fibrosis using SWE, FIB-4 score, and APRI. This reduction may be due to a reduction in fibrosis or the inhibition of HCV-induced hepatic inflammation and edema in hepatic tissue. This reduction is still not known whether it impacts the clinical status of the patient or not [6–8].

To our knowledge, few studies in our locality that assessed the effects of DAAs on the fibrosis degree, portal hemodynamics, and the clinical outcome after achieving SVR. In the current study, we tried to study the effects of DAAs on liver fibrosis, portal hemodynamics, and clinical outcomes.

Patients and methods

In our prospective longitudinal study, one hundred patients with chronic HCV-related liver cirrhosis who attended Al-Rajhi Liver Hospital, Assiut University, were enrolled in our study during the period between December 2018 and December 2021.

Inclusion criteria

Age 18–80 years old and HCV infection-related cirrhosis with Child–Pugh class (A & B).

Exclusion criteria

Child C liver cirrhosis, HCV co-infection with hepatitis B virus or HIV, contraindications to DAAs (pregnancy, lactation, hypersensitivity to one of the drugs in the treatment regimen), causes of chronic liver disease other than HCV, patients with hepatocellular carcinoma, and if the patient refused.

Sample size calculation

We obtained the reference value for the fibrosis stage regression according to poster 777 (in AASLD), 2015 [9]. For accurate calculation of the fibrosis stage, 98 patients would be included to achieve a 95% confidence interval and a width equal to 0.2. We enrolled 116 patients at the start of the study. Sixteen patients were lost for follow-up during the period of the study and 100 patients completed the follow-up period.

All patients were evaluated as regards the following:

Thorough history and clinical examination, abdominal ultrasound, Doppler ultrasound, share wave elastography (SWE), and laboratory investigations were done before therapy, 3 and 12 months after the end of therapy.

The laboratory investigations included HCV Ab, PCR for HCV RNA (quantitative), complete blood count, prothrombin time, INR, liver enzymes (alanine transaminase, aspartate transaminase), serum bilirubin, serum albumin, blood urea, serum creatinine, fasting blood sugar and HbA1c (if the patient is diabetic), HBs Ag, and alpha-fetoprotein.

Non-invasive laboratory fibrosis markers:

- FIB-4 score = Age (years) × AST (IU/L)/platelet count (109/L) × $\sqrt{}$ALT (IU/L) [10]
- AST/platelet ratio index (APRI) = [AST (IU/L)/AST upper limit of normal (IU/L)]/platelet count ($10.^9$/L) × 100 [11]

Abdominal ultrasound

- Abdominal ultrasonography was done at baseline and 3 and 12 months after the end of treatment. Liver size, echogenicity, surface of the liver, portal vein diameter, intrahepatic venous and biliary channels, splenic size, and ascites were reported and followed up.

Share wave elastography (SWE)

Assessment of liver stiffness by SWE was done with the Philips iU 22 ultrasonic apparatus (Bothell, WA, Elast PQ). After fasting for 3 h, the patients were examined in a supine position with a fully abducted right arm. The right lobe of the liver is examined through the intercostal spaces. Expression of liver stiffness was done in kilopascals (kPsc) according to the usual standard procedure. We used the following cutoff values for defining fibrosis stages: $F \geq 1, > 7.1$ kPa; $F \geq 2, > 7.8$ kPa; $F \geq 3, > 8$ kPa; and $F = 4, > 11.5$ kPa [12].

Portal hemodynamics (Doppler ultrasound)

In quiet respiration, the diameter of the portal vein was measured at the hepatic hilum just before branching into right and left. The two cursors were put in the internal wall of the portal vein, excluding the wall [13].

The B-mode gray scale was used to measure the portal vein diameter and cross-sectional area by scanning perpendicular to the long axis of the portal vein. Measurement was done midway between the confluence of the splenic and superior mesenteric vein, and bifurcation of the portal vein during quiet inspiration [14].

The portal vein velocities measured were the time average mean velocity. The software package of the ultrasound machine calculated TAMV electronically. PVV is measured by scanning the extrahepatic portal vein along its longitudinal axis [14].

The portal vein cross-sectional area and PVV were measured 3 times to reduce intra-observer variability, and the mean value was considered. The following formula was used to calculate the portal vein cross-sectional area:

$$\text{Cross-sectional area} = \frac{(A \times B) \times 3.14159}{4}$$

A is the longitudinal axis of the portal vein, B is the axial axis of the portal vein, and $\pi = 3.14159$ [15].

The resistive index (RI) is the ratio of the upstroke of the systolic wave in the hepatic artery to the end-diastolic flow rate, and normal RI should be 0.6 to 0.9 [16].

The "congestion index" is the ratio between the cross-sectional area (cm^2) and the PVV (cm/s) [15].

Treatment of HCV

All patients were given sofosbuvir (400 mg) and daclatasvir (60 mg) daily with or without ribavirin (weight-based) as a dual or triple therapy for 12 or 24 weeks, respectively, according to the guidelines of the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) [17].

Statistical analysis

We used the SPSS version 26 for Windows (SPSS Inc., Chicago, Illinois, USA). Quantitative data were presented as mean, SD, and ranges if their distribution was found to be parametric. Qualitative data were presented as numbers and percentages. To compare between two independent groups with qualitative data, χ^2 test and/or Fisher's exact test were used. Independent t test was used to compare two independent groups with quantitative data and parametric distribution. Repeated measures ANOVA is used when comparing more than two paired groups with quantitative data and parametric distribution. Pearson correlation was used to determine the correlation between non-invasive assessment of liver fibrosis and Doppler ultrasound findings. All statistical analyses were significant at a 0.05 level of probability ($P \leq 0.05$).

Results

Table 1 shows the baseline data of the studied patients. Most of our patients were males (65%) with a mean age of 60.9 ± 8.81 years. Smoking was reported in 57 (57%) patients, and the comorbidities found were diabetes mellitus 25 (25%) and hypertension 27 (27%). Most patients (89%) received SOF\DAC\RBV for 12 weeks, and only (11%) received SOF\DAC for 24 weeks due to low hemoglobin levels at a baseline of less than 10.5 g/dl (according to The Egyptian National Committee for Control of Viral Hepatitis). Regarding patients who underwent upper endoscopy, esophageal varices were found in 13 patients and portal hypertensive gastropathy "PHG" in 2 patients, while upper endoscopy was normal in 11 patients. The remaining patients refused to undergo upper endoscopy.

Table 2 shows the laboratory and ultrasound data of our patients before treatment and 3 and 12 months after the end of treatment. The most significant changes observed were in AFP, AST, ALT, serum albumin, and INR. Other laboratory parameters did not show significant changes. The mean values of AFP, AST, ALT, and INR were significantly decreased 3 and 12 months after the end of treatment compared to baseline. Also, the mean values of these parameters were significantly decreased 12 months after the end of treatment compared to 3 months after

Table 1 Baseline clinical data of our patients

Item	Descriptive "$n = 100$"
-Age "years"	
Mean ± SD	60.9 ± 8.81 (36–80)
-Sex	
Male	65 (65%)
Female	35 (35%)
-Smoking	57 (57%)
-Comorbidity	
Diabetes mellitus	25 (25%)
Hypertension	27 (27%)
-Treatment regimen	
SOF\DCV\RBV 12 weeks	89 (89%)
SOF\DCV 24 weeks	11 (11%)
-Baseline upper endoscopy (26 patients)	
Normal	11 (42.3%)
Varices	13 (50%)
Portal hypertensive gastropathy	2 (7.69%)

Data expressed as frequency (percentage), mean ± SD

SOF/DCV/RBV Sofosbuvir/Daclatasvir/Ribavirin

Table 2 Laboratory and ultrasound data of our patients before treatment and 3 and 12 months after the end of treatment

Item	Baseline (before treatment) "*n* = 100"	3 months After treatment "*n* = 100"	12 months after treatment "*n* = 100"	*P* value
Hemoglobin %	12.9 ± 2.57	12.25 ± 2.17 P1 = 0.275	11.77 ± 2.04 **P2 < 0.02***	***P* < 0.02*** P3 = 0.208
Red blood cells	4.7 ± 0.60	4.27 ± 0.54 P1 = 0.483	4.29 ± 0.713 P2 = 0.628	*P* = 0.087 P3 = 0.682
White blood cells	6.55 ± 0.35	6.18 ± 1.27 P2 = 0.492	3.94 ± 2.63 **P2 < 0.001****	***P* < 0.001**** **P3 < 0.001****
Platelets	155.5 ± 63.34	156.41 ± 69.46 P1 = 0.372	159.80 ± 72.56 P2 = 0.435	*P* = 0.106 P3 = 0.468
Urea	34.74 ± 7.64	34.82 ± 8.43 P1 = 0.573	34.93 ± 9.81 P2 = 0.708	*P* = 0.622 P3 = 0.429
Creatinine	0.94 ± 0.20	0.99 ± 0.41 P1 = 0.349	1.02 ± 0.14 P2 = 0.617	*P* = 0.103 P3 = 0.669
AFP	9.31 ± 1.22	5.21 ± 1.17 **P1 < 0.02***	3.85 ± 1.09 **P2 < 0.001****	***P* < 0.01*** **P3 < 0.03***
AST	63.36 ± 14.22	42.45 ± 10.46 **P1 < 0.001****	29.15 ± 6.33 **P2 < 0.000*****	***P* < 0.001**** **P3 < 0.000*****
ALT	59.89 ± 15.24	38.74 ± 11.24 **P1 < 0.001****	23.84 ± 8.64 **P2 < 0.000*****	***P* < 0.001**** **P3 < 0.001****
S. Bilirubin	0.932 ± 0.51	0.918 ± 0.34 P1 = 0.573	0.858 ± 0.16 P2 = 0.508	*P* = 0.482 P3 = 0.337
S. Albumin	3.67 ± 0.57	3.78 ± 0.48 P1 = 0.241	3.95 ± 0.47 **P2 < 0.01***	***P* < 0.01*** **P3 < 0.03***
INR	1.19 ± 0.19	1.17 ± 0.14 P1 = 0.248	1.14 ± 0.15 **P2 < 0.02***	***P* < 0.04*** **P3 < 0.03***
Ascites	9 (9%)	13 (13%)	1 (1%)	***P* < 0.001**** [$]

Data expressed as mean ± SD

ALT Alanine transaminase, *AST* Aspartate transaminase, *INR* International normalization ratio, *AFP* Alpha fetoprotein

P value was calculated using repeated measures ANOVA

* Significant difference $P < 0.05$

** Moderate significant difference $P < 0.001$

*** Highly significant difference $P < 0.000$

P: comparison between baseline and 3 and 12 months after the end of treatment

P1: comparison between baseline and 3 months after the end of treatment

P2: comparison between baseline and 12 months after the end of treatment

P3: comparison between 3 and 12 months after the end of treatment

[$] *P* value using chi-square test

the end of treatment. The mean value of serum albumin increased with moderate significance 12 months after the end of treatment compared to the baseline. All patients had criteria for liver cirrhosis. Splenomegaly was detected in 31% of cases. Nine patients (9%) had ascites before treatment. Three months after the end of treatment 13 patients had ascites (4 patients developed new onset ascites), while 12 months after the end of treatment only one patient had ascites. Only two cases developed hepatic focal lesions (diagnosed as hepatocellular carcinoma) 12 months after the end of treatment.

Table 3 shows the non-invasive biomarkers of liver fibrosis at baseline and follow-up. There was a significant decrease in all parameters used for the assessment of hepatic fibrosis. Regarding the FIB4 score, the mean score decreased from 3.93 at baseline to 3.28 3 months after treatment (19.81% decrease percentage) and then 2.89 12 months after treatment (26.46% decrease percentage) ($P < 0.01$). The degree of liver fibrosis measures by SWE showed also a significant decrease; the mean of baseline measurements was 19.8 kPa, while it was 15.88 kPa 3 months after treatment (19.79% decrease percentage) and it was 13.77 kPa 12 months after treatment (30.45% decrease percentage). The APRI also showed a statistically significant reduction. The mean score before therapy was 1.46, while 3 months after treatment, it was 1.13 (22.6% reduction), and 12 months after treatment, it was 0.86 (41.09% reduction) ($P < 0.001$). The number

Table 3 Non-invasive biomarkers of liver fibrosis at baseline and follow-up

Item	Baseline "*n* = 100"	3 months after the end of treatment "*n* = 100"	12 months after the end of treatment "*n* = 100"	*P* value
FIB4 (mean ± SD)	3.93 ± 2.78	3.28 ± 1.21 **P1 < 0.001****	2.89 ± 1.69 **P2 < 0.001****	***P* < 0.01*** **P3 < 0.01***
Stage of fibrosis				
• F3 • F4	0 100 (100%)	1(1%) 99(99%) **P1 = 0.678**	8(8%) 92(92%) **P2 < 0.04***	***P* < 0.02*** **P3 < .04***
SWE"KPa" (mean ± SD)	19.80 ± 7.90	15.88 ± 6.42 **P1 < 0.04***	13.77 ± 5.42 **P2 < 0.001****	***P* < 0.001 **** **P3 < 0.02***
APRI score	1.46 ± 0.42	1.13 ± 0.44 **P1 < 0.001****	0.86 ± 0.37 **P2 < 0.000*****	***P* < 0.001 **** **P3 < 0.02***

APRI AST/PLT ratio index, *SWE* Share wave elastography, *FIB4* Fibrosis score 4

P: comparison between baseline and 3 and 12 months after the end of treatment

P1: comparison between baseline and 3 months after the end of treatment

P2: comparison between baseline and 12 months after the end of treatment

P3: comparison between 3 and 12 months after the end of treatment

of patients who had stage F4 fibrosis decreased from 100 patients at baseline to 92 patients 12 months after the end of treatment. The remaining 8 patients showed improvement of their fibrosis stage (became F3).

Table 4 shows the Child–Pugh score, Child class, and MELD score of the studied patients before and after treatment. Significant improvement in Child–Pugh scores was observed. The number of patients in Child class-A increased from 79 at baseline to 90 and 94 patients 3 and 12 months after the end of treatment, respectively. The number of patients in Child class-B decreased from 21 patients before treatment to 7 and 5 patients 3 and 12 months after the end of treatment, respectively. At baseline, there were no Child class-C patients, but 3 patients became decompensated and their Child score was Child-C 3 months after the end of treatment; two of them showed improvement after 12 months of treatment and their Child score improved (became B)

Table 4 Follow-up in Child–Pugh score and Child class and MELD score in the study group

Item	Baseline "*n* = 100"	3 months after the end of treatment "*n* = 100"	12 months after the end of treatment "*n* = 100"	*P* value
MELD score	9.05 ± 1.03	8.65 ± 2.63 **P1 = 0.518**[b]	8.54 ± 2.27 **P2 = 0.338**[b]	***P* = 0.431**[a] **P3 = 0.738**[b]
Child–Pugh score	5.73 ± 1.03	5.45 ± 1.02* **P1 < 0.04***[b]	5.27 ± 0.91 **P2 < 0.03***[b]	***P* < 0.02***[a] **P3 = 0.276**[b]
Child class				
• A • B • C	79 (79%) 21 (21.0%) –	90 (90%) 7 (7%) 3 (1%) **P1 < 0.001****[c]	94 (94%) 5 (5%) 1 (1%) **P2 < 0.000*****[c]	**P < 0.000*****[c] **P3 = 0.376**[c]

[a] *P* value using repeated measurements test for numeric data

[b] *P*-value using Paired t-test test

[c] Chi-square test for non-numeric data

* Significant difference $P < 0.05$

** Moderate significant difference $P < 0.001$

*** Highly significant difference $P < 0.000$

P: comparison between baseline and 3, and 12 months after the end of treatment

P1: comparison between baseline and 3 months after the end of treatment

P2: comparison between baseline and 12 months after the end of treatment

P3: comparison between 3 and 12 months after the end of treatment

while the last patient did not show improvement at the end of our study period. No significant change in MELD score was observed in the present study ($P=0.43$).

Table 5 shows the changes in Doppler ultrasound of the portal vein and hepatic artery before and after treatment. There was a significant increase in portal vein flow velocity at follow-up (12 months after the end of treatment). There was also a significant decrease in TAMV 3 and 12 months after the end of treatment. There was a significant decrease in the cross-section area 12 months after the end of treatment. Regarding the hepatic arterial resistive index, no significant changes were observed during the follow-up period.

Table 6 shows the relation between Doppler ultrasound findings and upper endoscopy in the study group at baseline ($n=26$).

The mean value of portal vein blood flow velocity was significantly lower in cases with varices and PHG ($P<0.05$) when compared to cases with normal findings. However, the mean value of portal vein diameter was significantly higher in cases with varices and PHG ($P<0.02$). The mean value of TAMV was significantly lower in cases with varices and PHG compared to cases with normal findings ($P<0.001$).

Table 7 shows the correlations between noninvasive biomarkers of liver fibrosis with Doppler findings in the study group 12 months after the end of treatment. There were positive correlations between noninvasive biomarkers and portal vein flow velocity, portal vein diameter, TAMV, and cross-section area in Doppler in the study group ($P<0.05$).

Discussion

There is relative paucity in the literature about the effects of direct-acting antiviral drugs on liver fibrosis, portal hemodynamics, and clinical outcomes in cirrhotic patients who received these drugs for chronic HCV. This study was designed to evaluate these changes in the hepatic fibrosis degree, portal hemodynamics, and clinical outcomes in patients with liver cirrhosis after

Table 5 Doppler ultrasound studies of the portal vein and hepatic artery before and after treatment

Item	Baseline "*n* = 100"	3 months after the end of treatment "*n* = 100"	12 months after the end of treatment "*n* = 100"	*P* value
PV flow velocity (mean ± SD) "cm/s"	18.73 ± 1.64	20.17 ± 2.57 **P1 = 0.527**	20.38 ± 2.79 **P2 < 0.02***	***P* = 0.376** **P3 < 0.04***
PV diameter (mean ± SD)" cm"	1.46 ± 0.03	1.37 ± 0.02	1.19 ± 0.04	P = 0.267
TAMV (mean ± SD) "cm/s"	13.01 ± 5.08	7.55 ± 2.37 **P1 < 0.000****	8.09 ± 1.43 **P2 < 0.000****	***P* < 0.02*** **P3 = 0.248**
Cross-section area (mean ± SD) "cm^2"	1.15 ± 0.77	1.10 ± 0.61 **P1 = 0.481**	0.94 ± 0.34 **P2 = 0.211**	***P* < 0.01*** **P3 = 0.217**
Hepatic arterial resistive index (mean ± SD)	0.632 ± 0.10	0.621 ± 0.08 **P1 = 0.743**	0.622 ± 0.08 **P2 = 0.659**	***P* = 0.341** **P3 = 0.243**
Congestion index (mean ± SD)	0.061 ± 0.27	0.054 ± 0.24	0.046 ± 0.1	***P* < 0.001****

P value using paired t test

TAMV Time average mean velocity, *PV* Portal vein

P: comparison between baseline and 3 and 12 months after the end of treatment

P1: comparison between baseline and 3 months after the end of treatment

P2: comparison between baseline and 12 months after the end of treatment

P3: comparison between 3 and 12 months after the end of treatment

Table 6 The relation between Doppler ultrasound findings and upper endoscopy in the study group at baseline

Item	Normal upper endoscopy "*n* = 11"	Varices & PHG "*n* = 15"	*P* value
-Portal vein flow velocity (mean ± SD)" cm/s"	21.99 ± 7.86	18.40 ± 4.09	***P* < 0.03***
-Portal vein diameter (mean ± SD) "cm"	1.16 ± 0.39	1.73 ± 0.30	***P* < 0.02***
-TAMV (mean ± SD) "cm/s"	9.62 ± 5.07	5.01 ± 2.41	***P* < 0.001****
-Cross-section area (mean ± SD) "cm^2"	1.18 ± 0.78	1.45 ± 0.57	*P* = 0.710
-Hepatic arterial resistive index (mean ± SD)	0.65 ± 0.11	0.639 ± 0.07	*P* = 0.449

P value using independent *t* test

TAMV Time average mean velocity

Table 7 Correlation between noninvasive biomarkers of liver fibrosis with Doppler findings in the study group 12 months after the end of treatment

		FIB4	APRI score	SWE
Portal vein flow velocity "cm/sec"	*r*	0.425	0.384	0.320
	p	**0.03***	**0.03***	**0.04***
Portal vein diameter "mm"	*r*	0.511	0.481	0.641
	p	**0.02***	**0.03***	**0.03***
TAMV "cm/s"	*r*	0.734	0.397	0.364
	p	**0.03***	**0.04***	**0.04***
Cross-section area "cm^2"	*r*	0.153	0.228	0.664
	p	**0.02***	**0.04***	**.03***
Hepatic arterial resistive index	*r*	0.162	0.216	0.046
	p	0.346	0.672	0.273

P value using Pearson's correlation *r*: correlation coefficient

achieving SVR. To our knowledge, this study is one of the few studies to combine clinical, laboratory, imaging, and endoscopic modalities to evaluate the effect of DAAs on the cirrhotic liver.

The results of our study showed that there was a decrease in the levels of liver enzymes (AST and ALT) and an increase in serum albumin level from baseline level to 3 and 12 months after the end of treatment. This is consistent with the study of Hablass et al. who reported a reduction of liver enzymes and serum bilirubin, an increase in serum albumin, and an improvement in INR after achieving SVR with DAAs [18]. Reddy et al. [19] also concluded that DAAs improved liver functions during a short-term follow-up specifically an increase in serum albumin. The same results were concluded in a short-term follow-up in many other studies [20, 21].

In our study, we found a significant reduction in the degrees of fibrosis after treatment measured by SWE, FIB-4 score, and APRI index in almost all patients. This agrees with Fouad et al. study [22] who found a significant reduction of liver stiffness after 12 weeks of the end of DAA therapy. Elsharkawy et al. in their study [23] reported a 22% improvement in the fibrosis degrees in all fibrosis stages using FibroScan. They also found 81.5% and 93% reductions in FIB4 and APRI scores, respectively. Similarly, our results indicated that the APRI index and FIB-4 score decreased gradually after achieving SVR. This suggests that eradication of HCV may lead to a decrease in the degree of fibrosis and hence the APRI and FIB-4 scores. This reduction is due to a reduction of liver enzymes after treatment that we noticed in our study. Laursen et al. [24] investigated the effects of DAA therapy on hepatic inflammation and fibrosis. They used plasma sCD163 and sMR levels (ELISA) for the assessment of inflammation, transient elastography for the measurement of liver stiffness and galactose elimination capacity for the assessment of liver function. They found a significant reduction in transient elastography readings by about 20% at the end of treatment with early reduction of liver inflammation evidenced by reduction of serum liver enzymes twelve weeks after the end of treatment.

From these data, the improvement in the degree of fibrosis using these noninvasive measures can be attributed to reduced liver enzymes (inflammation) and/or due to real decrease in fibrosis severity. The marked reduction of the APRI and FIB4 scores may be impacted by the marked improvement of the liver enzymes which is agreed upon by Fouad et al. [22].

In our study, Child–Pugh score improved significantly, 12 months after the end of treatment. Child A was (79%) before treatment and became (94%) 12 months after the end of treatment. Child B patients were (21%) before treatment and became (5%) after treatment. There were no Child C cases before treatment. Only one patient decompensated and became Child C 12 months after the end of treatment with a highly statistically significant difference. This improvement is due to improvement in INR, S. Albumin, and S. Bilirubin. In their study, Ali et al. [25] reported improvement in liver functions (ALT, AST, bilirubin, prothrombin time, and INR, with significant elevation of serum albumin) in HCV patients who achieved SVR compared to those who failed to achieve SVR. The Child score however was not found to improve in these patients. In other previous studies, there were variable degrees of improvement in Child scores from 64 to 87% in Child class-B and class-C cirrhosis [26, 27].

Regarding the MELD score, our results showed a nonsignificant difference in the MELD score between baseline and 12 months after the end of treatment. Berge et al. [28] found also the same results. This may be explained by the fact that only patients with lower MELD scores are candidates for treatment and those with higher scores are not candidates. In contrast, some other authors [26, 27] found variable degrees of improvement in MELD scores from 50 to 83%. This may be due to the treatment of patients with decompensated liver disease with higher MELD and Child score that shows more considerable and significant changes after treatment.

In our study, we found significant improvement in Doppler ultrasound parameters (portal vein blood flow velocity and time average mean velocity) after treatment. Also, there was an improvement in portal vein diameter and cross-section area 12 months after the end of treatment. This change is due to a decrease in fibrosis and its impact on portal hypertension post-treatment with DAAs. This agrees with Hassnine et al. [29] who used portal vein Doppler findings, as indicators for portal hypertension, after achieving SVR.

The reduction in the SWE readings and the improvement in Doppler ultrasound parameters together with the reduction in Fib-4 score and APRI in our study confirms that there is a reduction in the degree of fibrosis and not only due to a reduction of liver enzymes.

In the present study, there was no correlation between Doppler parameters and non-invasive biomarkers at baseline (before treatment), but there was a positive correlation between Doppler parameters with noninvasive biomarkers 12 months after the end of treatment. This agrees with Elwan et al.'s study [30] who found that Fibroscan parameters in moderate fibrosis were positively correlated with Doppler parameters ($P < 0.001$).

In our study, two patients developed HCC 12 months after the end of treatment (2%), and our findings matched with Nappi et al.'s [31] who reported the occurrence of HCC in 6 out of 241 patients achieved SVR (2.3%). The mean interval before the diagnosis of HCC was 18.5 months after the end of treatment. All patients who developed de novo HCC had F4 fibrosis before treatment of HCV. In his study, all HCC cases were among those who were treated with a SOF-based regimen. Despite being F4, none of the patients who failed to achieve SVR developed HCC.

The higher the success rate of DAAs in achieving SVR, the fewer the side effects, and the positive impact of these agents in improving the degree of fibrosis, with its clinical impact in improving the clinical and laboratory parameters; all these advantages make DAAs as an ideal treatment especially in early stages of chronic HCV-related liver disease [27, 32].

Conclusion

DAAs are safe and effective in the treatment of HCV infection even in the presence of liver cirrhosis. DAAs use leads to viral eradication, improvement of liver functions, improvement in noninvasive markers of fibrosis and Child–Pugh score and class. Significant improvement in the mean value of liver fibrosis (assessed by noninvasive biomarkers, FIB4, liver stiffness, APRI) was observed at 3 and 12 months after the end of treatment.

Limitations

The relatively short period of follow-up is one of the limitations of our study. The improvement of fibrosis may need a longer time to be more evident. The relatively small sample size is another limitation.

Abbreviations

SWE	Shear wave elastography
DAA	Direct-acting agents
HCC	Hepatocellular carcinoma
SVR	Sustained virological response
CHC	Chronic hepatitis C infection
TAMV	Time average mean velocity
PVV	Portal vein flow velocity

Acknowledgements

Not applicable.

Authors' contributions

WAH participated in the design of the study and coordination of the work and drafted the manuscript. SIK participated in the design of the study, revised the statistical analysis, and helped in drafting the manuscript. IAM participated in the design of the study, curation of patients, and data entry. NM performed the statistical analysis and helped in drafting the manuscript. MM participated in the study design and performed the Doppler study. SMH participated in the design of the study and performed share wave elastography. All authors read and approved the final manuscript.

Funding

We did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit organizations.

Availability of data and materials

All datasets on which the conclusions of the manuscript rely are presented in the main paper.

Declarations

Ethics approval and consent to participate

The study protocol was registered at ClinicalTrials.gov ID: NCT03241823. Our study was approved by the Medical Ethics Committee of the Institutional Review Board of the Faculty of Medicine, Assiut University, Egypt.

Consent for publication

We obtained written consent from all participants according to the Declaration of Helsinki.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assiut University, Assiut 71515, Egypt. [2]Department of Diagnostic Radiology, Faculty of Medicine, Assiut University, Assiut 71515, Egypt.

Received: 31 March 2023 Accepted: 21 September 2023
Published online: 02 October 2023

References

1. Han R, Zhou J, François C et al (2019) Prevalence of hepatitis C infection among the general population and high-risk groups in the EU/EEA: a systematic review update. BMC Infect Dis 19(1):655. https://doi.org/10.1186/s12879-019-4284-9. PMID: 31337339; PMCID: PMC6647266.
2. World Health Organization. (2022) Fact sheet. Available online: https://www.who.int/news-room/fact-sheets/detail/ hepatitis-c.
3. Roche B, Coilly A, Duclos-Vallee et al (2018) The impact of treatment of hepatitis C with DAAs on the occurrence of HCC. Liver Int 38(Suppl 1):139–145. https://doi.org/10.1111/liv.13659
4. Scaglione V, Mazzitelli M, Costa C et al (2020) Virological and clinical outcome of DAA containing regimens in a cohort of patients in Calabria Region (Southern Italy). Medicina (Kaunas) 56(3):101. https://doi.org/10.3390/medicina56030101
5. European Association for the Study of the Liver (2020) EASL recommendations on treatment of hepatitis C: final update of the series☆. J Hepatol 73(5):1170–1218. https://doi.org/10.1016/j.jhep.2020.08.018
6. Yoo HW, Park, (2022) Regression of liver fibrosis and hepatocellular carcinoma development after HCV eradication with oral antiviral agents. Sci Rep 12(1):193. https://doi.org/10.1038/s41598-021-03272-1

7. Hassanin T, Ibraheem H, Makhlouf M et al (2022) Non-invasive evaluation of liver fibrosis changes in patients with chronic hepatitis C after directly acting antiviral drugs. Afro-Egyptian Journal of Infectious and Endemic Diseases 12(1):92–98. https://doi.org/10.21608/aeji.2022.108490.1194
8. Elsharkawy A, Samir R, El-Kassas M (2022) Fibrosis regression following hepatitis C antiviral therapy. World J Hepatol 14(6):1120–1130. https://doi.org/10.4254/wjh.v14.i6.1120
9. Poster Session 2: advances in imaging and noninvasive markers of fibrosis; Bile Acids, Cholangiocyte Biology, and Experimental Cholestasis. 2015;62:594A-624A. https://doi.org/10.1002/hep.28218.
10. Sterling RK, Lissen E, Clumeck N et al (2006) Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology (Baltimore, MD) 43(6):1317–1325. https://doi.org/10.1002/hep.21178
11. Wai CT, Greenson JK, Fontana RJ et al (2003) A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology (Baltimore, MD) 38(2):518–526. https://doi.org/10.1053/jhep.2003.50346
12. Sporea I, Bota S, Gradinaru-Taşcău O et al (2014) Which are the cut-off values of 2D-shear wave elastography (2D-SWE) liver stiffness measurements predicting different stages of liver fibrosis, considering transient elastography (TE) as the reference method? Eur J Radiol 83(3):e118–e122. https://doi.org/10.1016/j.ejrad.2013.12.011
13. Geleto G, Getnet W, Tewelde T (2016) Mean normal portal vein diameter using sonography among clients coming to Radiology Department of Jimma University Hospital, Southwest Ethiopia. Ethiop J Health Sci 26(3):237–242. https://doi.org/10.4314/ejhs.v26i3.6
14. Ibinaiye PO, Aiyekomogbon JO, Tabari MA, Chom ND, Hamidu AU, Yusuf R (2015) Determination of normal portal vein parameters on triplex ultrasound scan among adults in Zaria, Nigeria. Sub-Saharan Afr J Med 2:33–38
15. Moriyasu F, Nishida O, Ban N et al (1986) "Congestion index" of the portal vein. AJR Am J Roentgenol 146(4):735–739. https://doi.org/10.2214/ajr.146.4.735
16. Caiado AH, Blasbalg R, Marcelino AS et al (2007) Complications of liver transplantation: multimodality imaging approach. Radiographics 27(5):1401–1417. https://doi.org/10.1148/rg.275065129
17. El-Akel W, El-Sayed MH, El Kassas M et al (2017) National treatment programme of hepatitis C in Egypt: Hepatitis C virus model of care. J Viral Hepatitis 24(4):262–267. https://doi.org/10.1111/jvh.12668
18. Hablass FH, Lashen SA, Mohamed EA (2021) Liver fibrosis regression after direct-acting antivirals for hepatitis C virus: a prospective study. J Gastroenterol Hepatol Res 10(1):3429–3434
19. Reddy KR, Lim JK, Kuo A et al (2017) All-oral direct-acting antiviral therapy in HCV-advanced liver disease is effective in real-world practice: observations through HCV-TARGET database. Aliment Pharmacol Ther 45(1):115–126. https://doi.org/10.1111/apt.13823
20. Jacobson IM, Poordad F, Firpi-Morell R et al (2019) Elbasvir/grazoprevir in people with hepatitis C genotype 1 infection and Child-Pugh class B cirrhosis: the C-SALT study. Clin Transl Gastroenterol 10(4):e00007. https://doi.org/10.14309/ctg.0000000000000007
21. Agwa RH, Elgazzar MH, El-Zayyadi IA et al (2022) Effect of sustained virological response after direct-acting antivirals on liver fibrosis in patients with chronic HCV infection. Egypt J Intern Med 34:18. https://doi.org/10.1186/s43162-022-00111-1
22. Fouad R, Elsharkawy A, Abdel Alem S et al (2019) Clinical impact of serum α-fetoprotein and its relation on changes in liver fibrosis in hepatitis C virus patients receiving direct-acting antivirals. Eur J Gastroenterol Hepatol 31(9):1129–1134. https://doi.org/10.1097/MEG.0000000000001400
23. Elsharkawy A, Eletreby R, Fouad R et al (2017) Impact of different sofosbuvir based treatment regimens on the biochemical profile of chronic hepatitis C genotype 4 patients. Expert Rev Gastroenterol Hepatol 11(8):773–778. https://doi.org/10.1080/17474124.2017.1326816
24. Laursen TL, Siggaard CB, Kazankov K et al (2020) Time-dependent improvement of liver inflammation, fibrosis and metabolic liver function after successful direct-acting antiviral therapy of chronic hepatitis C. J Viral Hepatitis 27(1):28–35. https://doi.org/10.1111/jvh.13204
25. Nada A, Ata L, Amer A et al (2022) Impact of long-term eradication of chronic Hepatitis C infection using the direct-acting antiviral treatment on liver fibrosis parameters in Egyptian patients. Med J Viral Hepatitis 7.1(1):21–32. https://doi.org/10.21608/mjvh.2022.279334
26. Charlton M, Everson GT, Flamm SL et al (2015) Ledipasvir and Sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 149(3):649–659. https://doi.org/10.1053/j.gastro.2015.05.010
27. Manns M, Samuel D, Gane EJ et al (2016) Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis 16(6):685–697. https://doi.org/10.1016/S1473-3099(16)00052-9
28. Berge E, Ana A, Elena O et al (2017) Clinical outcomes of direct-acting antiviral therapy in patients with compensated hepatitis C virus-related cirrhosis. Hepatoma Res 3:209–214. https://doi.org/10.20517/2394-5079.2017.28
29. Hassnine A, Soliman W, Elsayed A et al (2022) Effect of direct-acting antiviral drugs on portal circulation hemodynamics in cirrhotic patients infected with HCV. Egypt Liver J 12:17. https://doi.org/10.1186/s43066-022-00181-4
30. Elwan N, Hemisa M, Soliman H et al (2021) Doppler ultrasound and fibroscan parameters versus liver biopsy in evaluation of hepatic fibrosis in Egyptian patients with chronic hepatitis C. Afro-Egypt J Infect Endem Dis 11(2):186–198. https://doi.org/10.21608/aeji.2021.55780.1127
31. Nappi A, Perrella A, Rinaldi L et al (2019) Late HCC onset after DAAs therapy in patients with SVR: a type D ADR that requires a longer follow-up? Eur J Hosp Pharm 26(4):243–244. https://doi.org/10.1136/ejhpharm-2019-001975
32. Wu DB, Jiang W, Wang YH et al (2019) Safety and efficacy of sofosbuvir-based direct-acting antiviral regimens for hepatitis C virus genotype 6 in Southwest China: real-world experience of a retrospective study. J Viral Hepatitis 26(3):316–322. https://doi.org/10.1111/jvh.13033

Publisher's Note