Effect of direct-acting antivirals on elastographic measures in patients with chronic hepatitis C virus infection

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Background
Hepatitis C virus (HCV) infection is a worldwide health problem. Liver fibrosis has been a major topic of research for decades. However, recent data have shown the occurrence of fibrosis fall in a wide spectrum of chronic liver diseases.
Aim
We aimed to evaluate the changes in transient elastography (TE) values of different direct-acting antivirals regimens in HCV chronic liver disease patients.
Settings and design
This observational analytic study was carried out at the Internal Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.
Participants and methods
100 Egyptian chronic hepatitis C patients were recruited into this study. All participants were included according to the inclusion criteria approved by the national committee in Egypt for control of viral hepatitis. They were subjected to a thorough assessment of history and clinical examination, routine investigations, ECG, radiological examination, and TE 2 weeks before treatment initiation, at the end of the course, and 6 months after treatment.
Results
There was a significant improvement in liver stiffness (LS) values in cirrhotic patients, but they still had cirrhosis, with lower LS values than pretreatment values. This study reported a significant decrease 12 weeks after the end of treatment for LS measurements and validated fibrosis scores such as FIB-4 and APRI. Patients with F4 grade fibrosis showed a significant improvement in the score, and the percentage decreased from 56% before treatment to 42 and 38% after sustained virological response 1 and sustained virological response 2, respectively.
Conclusion
Direct-acting antivirals based treatment results in a significant improvement in hepatic fibrosis measures, indicated by TE as well as noninvasive fibrosis scores such as fibrosis score (FIB-4) and APRI.

Keywords:
direct-acting antivirals, hepatitis C virus, transient elastography

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Introduction

Hepatitis C virus (HCV) is a worldwide problem and is considered to be one of the major causes of morbidity and mortality related to liver disease [1].

Egypt has the highest prevalence rate of HCV in the world. About 14.7% of the Egyptian population has HCV antibodies [2] and 9.8% has an active infection [3].

Acute HCV infection is usually asymptomatic and about 75% of cases progress to a chronic state leading to chronic HCV infection [4].

Treatment of HCV has been revolutionized with the introduction of direct-acting antiviral (DAAs) therapies in 2014/2015, with a higher sustained virological response (SVR) rate, short simplified regimens, and minimal treatment-related side effects [5].

Retrograding of liver fibrosis has been a major topic of research and discussion in the community of liver experts for decades. However, recent data have shown the occurrence of fibrosis fall in a wide spectrum of chronic liver diseases including viral hepatitis [6].

Several studies have reported that regression of liver fibrosis by using potent antiviral agents in chronic hepatitis C patients can be achieved by improving hepatic necroinflammation provocative injury in sustained responders and speed progression in those who develop relapse [7].

Nowadays, transient elastography (TE) is used as a valid noninvasive method for assessing hepatic fibrosis in HCV patients with the advantage of considerable accuracy and reproducibility [6].

Furthermore, the utility of TE has been evaluated in observing progression of fibrosis within the setting of HCV repetition after liver transplantation [8].

This study was designed to determine changes in TE values of various DAAs regimens in HCV chronic liver disease patients.

Aim

We aimed to evaluate changes in TE values of different DAAs regimens in HCV chronic liver disease patients.

Patients and methods

This observational analytic study was carried out at the Internal Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt, from April 2017 to April 2018 and included a total of 100 Egyptian chronic hepatitis C patients. They were subjected to a thorough assessment of history and clinical examination, routine investigations, ECG, radiological examination, and TE within 2 weeks before treatment initiation and 6 months after the termination of treatment.

Inclusion criteria

All eligible patients were included according to the inclusion criteria approved by the national committee in Egypt for control of viral hepatitis (NCCVH, 2015).

(1) Age from 18 to 75 years – HCV RNA positivity.
(2) Treatment naïve or experienced – any stage of fibrosis.

Exclusion criteria

(1) Patients with hypersensitivity to the drugs used.
(2) Pregnancy or inability to use effective contraception.
(3) Albumin less than 2.8.
(4) International normalization ratio (INR) more than 1.7.
(5) Total bilirubin more than 3.
(6) Platelets less than 50 000.
(7) Hepatocellular carcinoma (HCC) except 4 weeks after the intervention aiming at a cure, with no evidence of activity by dynamic imaging (clotting time (CT) or MRI).
(8) Extrahepatic malignancy, except after 2 years of disease-free intervals. In cases of lymphomas and chronic lymphocytic leukemia, treatment can be initiated immediately after remission on the basis of the treating oncologist's report.
(9) Patients with poorly controlled diabetes mellitus (HbA1c>9%).

Ethical clearance

Written informed consent was obtained from the patients for participation in the study. Approval for the study was obtained from the General Medicine Department, and the IRB unite in Zagazig university Hospital.

All participants were subjected to the following:

(1) Assessment of history:
   (a) Thorough assessment of history was performed to exclude any history of hepatic encephalopathy, ascites, or history of previous endoscopies and upper gastro intestinal tract (GIT) bleeding.
   (b) Review of other comorbidities and drug history was performed to exclude drug–drug interactions.
(2) Routine laboratory investigations that included the following:
   Complete blood picture, liver function tests: serum bilirubin (total and direct), serum albumin, serum ALT and AST, serum creatinine. Coagulation profile: prothrombin time (PT), prothrombine concentration (PC) and INR. Fasting blood sugar, HbA1c, Alpha feto protien (AFP), HBsAg, HCV RNA Quantitative PCR, and pregnancy test for women in childbearing periods.
(3) ECG: ECHO and reports from the cardiologist were requested from patients with ischemic heart disease (IHD) or ischemic changes in ECG.
(4) Radiology:
   (a) Pelvi-abdominal ultrasound.
   (b) Triphasic CT if HCC supposed AFP more than 100 ng/ml and for patients who have undergone a radical curative intervention for HCC (resection or successful local ablation).
   (c) TE within 2 weeks before treatment initiation, at the end of the course, and 6 months after termination of treatment using (Fibroscan R, Echosens, France) [9].

Follow-up during the study period included the following:

(1) Clinical examination to detect the development of signs of liver decompensation or any side effect of the treatment regimens.
(2) HCV RNA quantitative PCR at the top of the treatment and 12 weeks once the End of treatement.
(3) Complete blood count, AST, ALT, total bilirubin at 4, 8, and 12 weeks of treatment.
(4) Fibroscan to detect the effects of DAAs treatment on liver fibrosis, at the end of the course, and 6 months after treatment.

Statistical analysis

Variables were processed and analyzed using SPSS version 20 (SPSS Inc., Chicago, IL, USA).

Results

This study included 100 Egyptian patients with HCV genotype 4 infection. Fifty-six (56%) patients were women, mean age 53.2 years. Only eight (8%) participants had received previous treatment for HCV, whether interferon or sofosbuvir based. In terms of comorbidities, 10 (10%) patients were hypertensive and 12 (12%) patients were diabetic (Table 1).

There was a statistically significant difference over the periods of study in total bilirubin (T.Bil), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum albumin (S. Alb), Alkaline phosphatase (Alk), and pH and AFP, Haemoglobin (Hb), platelet count, and White Blood Cells (WBCs) in the study group. All patients, whether cirrhotic or not, showed a statistically significant decrease in the previous laboratory parameters and a marked improvement was detected after 3 months of termination of DAAs treatement (ttt) (SVR1) and 6 months after the end of the course (SVR2) (Table 2).

Table 3 shows a highly significant improvement in the TE measures, fibrosis score (FIB-4), and the APRI score throughout the study period, which indicates significant overall regression of liver fibrosis after SVR1 and SVR2.

Patients with F4 grade fibrosis showed a significant improvement in the FIB-4 score, and the percentage decreased from 56% before treatment to 42 and 38% after SVR1 and SVR2, respectively (Table 4).

Table 5 shows a positive correlation between TE measures, FIB-4 and APRI, using the Pearson correlation coefficient in the study group at 3 and 6 months of the end of treatment by Direct Acting Antivirals treatement.

Table 6 shows that the sensitivity of FIB-4 in the prediction of TE measures was 50%, specificity was 92.9%, positive predictive value (PPV) was 94.7%, negative predictive value (NPV) was 41.9%, and accuracy was 62%. Also, the sensitivity of the APRI score in the prediction of TE measures was 86.1%, specificity was 64.3%, PPV was 86.1%, NPV was 64.3%, and accuracy was 80%.

The sensitivity of TE measures in the prediction of liver fibrosis was 72% and that for FIB-4 was 38%. On using both TE measures and the FIB-4 score in the prediction of liver fibrosis, the sensitivity rate increased to 74%. On using both TE measures and the APRI score, the percentage of sensitivity increased to 82% (Table 7).

Table 1 Demographic characteristics of the study group

Age	
Range	18–70
Mean±SD	53.22±9.60
Sex (male/female) (%)	44–56
Previous treatment experience (%)	8
DM (%)	12
HTN (%)	10

DM, diabetes melletus; HTN, hypertension.

Discussion

DAAs regimens were introduced by the Ministry of Health in Egypt as part of a national treatment program for Chronic Hepatitis C (CHC) patients in the second half of 2014, where all eligible patients were treated with DAAs according to the approved treatment recommendation [10].

Higher rates of SVR and improvement in liver fibrosis are the major goals for CHC treatment. It is postulated that the achievement of SVR would result in the resolution of liver fibrosis, and this would play a role in reducing the risk of liver-related complications such as hepatic decompensation, variceal bleeding, and HCC [11].

The current anti-HCV therapies were not designed to be anti-fibrotic, but focused on virus eradication as HCV is a composite indicator of liver fibrosis and a causative agent of liver injury and inflammation [12].

TE has been used to monitor potential regression of liver pathology after antiviral treatment and may

Table 2 Biochemical changes among the studied population before, after 3 months, and after 6 months of treatment in the studied population

Biochemical changes	Before	After 3 months	After 6 months	ANOVA	*P* value
T.Bil. (mg/dl)					
Range	0.1–2.9	0.1–2.8	0.3–2.6	2.669	0.009
Mean±SD	1.21±0.71	1.04±0.61	1.07±0.56		
SGOT (U/l)					
Range	18–321	12–86	15–63	9.481	<0.001
Mean±SD	66.82±49.53	33.32±15.78	31.08±12.06		
SGPT (U/l)					
Range	12–159	10–90	9–129	6.665	<0.001
Mean±SD	51.26±32.06	25.20±15.70	27.16±18.32		
S.Alb (g/dl)					
Range	2.9–5	2.9–4.9	3–5.2	–1.190	0.237
Mean±SD	3.72±0.61	3.67±0.56	3.78±0.55		
INR					
Range	0.9–1.25	0.99–1.31	1.09–1.38	–1.498	0.109
Mean±SD	1.13±0.18	1.21±0.16	1.29±0.15		
Alk. pH (U/l)					
Range	38–452	38–429	1–374	3.825	<0.001
Mean±SD	155.3±101.5	133.98±78.65	123.14±71.87		
AFP (ng/ml)					
Range	0.7–33.50	0.5–87	1.8–17.6	2.264	0.026
Mean±SD	9.29±6.83	6.97±6.11	5.88±3.48		
Hb (g/dl)					
Range	8.7–16.9	7.8–17.4	8.6–19.2	2.592	0.011
Mea±SD	13.11±1.91	12.36±2.03	12.71±1.69		
Platelets ($n\times10^3/cm^2$)					
Range	59–375	40–421	44–431	3.194	0.002
Mean±SD	154.18±91.7	147.17±89.86	139.88±83.39		
WBC ($n\times10^3/cm^2$)					
Range	1.7–11	1.7–9.8	1.5–10	2.889	0.042
Mean±SD	5.05±2.12	4.99±1.92	4.75±1.80		
S. Creat (mg/dl)					
Range	0.4–1.55	0.5–1.45	0.48–1.5	0.847	0.399
Mean±SD	0.82±0.23	0.78±0.23	0.80±0.22		

AFP, alpha feto protien; ALk, Alkaline phosphatase; ANOVA, ANOVA score system; Hb, haemoglobin; INR, international normalization ratio; S.Alb, serum albumin; S. Creat, serum creatinine; SGOT, serum glutamic oxaloacetic transaminase; T.Bil, total bilirubin.

Table 3 Transient elastography, FIB-4 score, and APRI score measurements before, after 3 months, and after 6 months of treatment in the studied population

	Before	After 3 months	After 6 months	ANOVA	*P* value
Transient elastography					
Range	4.5–75	4–75	4–75	5.904	<0.001**
Mean±SD	29.42±20.20	24.59±19.27	23.63±19.88		
FIB-4 score					
Range	0.32–46.28	0.25–24.4	0.31–13.37	2.607	0.011*
Mean±SD	5.27±4.02	3.80±2.83	3.63±2.93		
APRI score					
Range	0.26–11.89	0.21–6.7	0.25–3.98	4.723	<0.001**
Mean±SD	1.81±1.08	1.19±1.09	1.17±0.87		

ANOVA, ANOVA score system; FIB-4, fibrosis score. *significant. **highly significance.

predict the treatment outcome of chronic hepatitis C as shown in several clinical studies [13].

However, few studies have explored the role of TE in detecting the dynamics of liver fibrosis and changes in liver stiffness (LS) in CHC patients who achieved an SVR following DAAs therapies [14].

We aimed to evaluate the impact of sofosbuvir-based regimens without interferon (IFN) on LS measures as

Table 4 Changes in the grade of fibrosis as indicated by transient elastography measures and FIB-4 score throughout the study period

	Before	After 3 months	After 6 months	χ^2	*P* value
Grade of fibrosis by transient elastography measures					
F0	4 (4)	14 (14)	18 (18)	12.337	0.015
F1	14 (14)	10 (10)	8 (8)		
F2	2 (2)	0	2 (2)		
F3	10 (10)	8 (8)	14 (14)		
F4	70 (70)	68 (68)	58 (58)		
Grade of fibrosis by FIB-4					
F0	24 (24)	18 (18)	18 (18)	13.304	0.002*
F2	20 (20)	40 (40)	44 (44)		
F4	56 (56)	42 (42)	38 (38)		

FIB-4, fibrosis score. *significant.

Table 5 Correlation between transient elastography measures, FIB-4 and APRI, using the Pearson correlation coefficient in the study group 3 and 6 months after the end of treatment

Transient elastography measures	After 3 months	After 6 months
FIB-4		
R	0.371	0.382
P value	<0.001	<0.001
APRI		
R	0.320	0.327
P value	<0.001	<0.001

FIB-4, fibrosis score.

assessed by TE and liver fibrosis measures as determined by FIB-4 and APRI scores.

To achieve this goal, we recruited 100 Egyptian chronic hepatitis C patients from the Internal Medicine Department, Zagazig University Hospitals, and the Viral Hepatitis Unit, Ahmed Maher Teaching Hospital, Ministry of Health, Cairo. All eligible participants were included according to the inclusion criteria approved by the national committee in Egypt for the control of viral hepatitis (NCCVH, 2015).

Similar to Bachofner *et al.* [15], who observed a reduction in APRI scores and the FIB-4 index after HCV eradication, our study reported a significant decrease twelve weeks after the end of treatment in LS measurements and validated fibrosis scores such as FIB-4 and APRI. In our study group, patients with F4 grade fibrosis showed a significant improvement in the score, and the percentage decreased from 56% before treatment to 42 and 38% after SVR1 and SVR2, respectively.

According to the FIB-4 score, 6% of patients started with F0 regressed to a higher grade. Consequently, patients with F2 Improved from 20 to 40 and 44% after SVR1 and SVR2, respectively.

These scores are affected by the reduction in AST, ALT, and platelet levels, indicating a significant improvement in liver fibrosis and necroinflammation following sofosbuvir treatment. Also, sustained responders showed a significant reduction in these scores.

Also, our study results showed a marked decrease in liver fibrosis grades using TE measures. The study found that the percentage of patients with F0 (no fibrosis) increased significantly from 4% before treatment to 14 and 18% after 3 months (SVR1) and 6 months (SVR2), respectively. Participants with F1 decreased from 14 to 8%. Regression from F4 to F3 was observed in 2% patients after 3 months (SVR1) and in 12% of patients after 6 months from treatment (SVR2). Patients with F2 grade failed to show any changes in the grade of fibrosis. However, patients with F3 decreased from 10 to 8% after 3 months (SVR1) and the percentage increased again to 14% after 6 months from treatment (SVR2).

These results are similar to those of a meta-analysis carried out by Akhtar *et al.* [16], in which out of 443 patients, 137 achieved SVR and cirrhosis was found to regress in about 53% of the patients as documented by liver biopsy pretreatment and a follow-up biopsy after treatment.

Improvement in LS measurements occurs early after therapy (12 weeks after end of treatement (EOT)) irrespective of the treatment outcome as the temporary reduction in viral replication may be sufficient to lower LS measurement. This early reduction in LS measurement following Direct Acting Antivirals treatement remains questionable in

Table 6 Overall validity of FIB-4 and APRI score transient elastography measures

	Grade of transient elastography measures [*N* (%)]		χ^2	*P* value
	Positive	Negative		
Grade of FIB-4				
Positive	36 (50)	2 (7.1)	15.717	<0.001
Negative	36 (50)	26 (92.9)		
Total	72 (100)	28 (100)		
APRI score				
Positive	62 (86.1)	10 (35.7)	25.398	<0.001
Negative	10 (13.9)	18 (64.3)		
Total	72 (100)	28 (100)		

FIB-4, fibrosis score.

Table 7 Sensitivity of transient elastography measures, FIB-4, and APRI in the assessment of liver fibrosis

	Positive [*N* (%)]	Negative [*N* (%)]
Grade of transient elastography measures	72 (72)	28 (28)
Grade of FIB-4	38 (38)	62 (62)
Grade of transient elastography measures and grade of FIB-4	74 (74)	26 (26)
Grade of transient elastography measures and APRI score	82 (82)	18 (18)

FIB-4, fibrosis score.

terms of whether this reduction represents an actual improvement in liver fibrosis or is a result of a reduction in liver inflammation because of antiviral treatment.

However, the influence of inflammation on the LS assessment is debatable. Some studies suggested that LS increased with increasing necroinflammatory activity of liver [17] and the resolution of this necroinflammatory activity correlated with transaminases that normalize following antiviral therapy, whereas other studies have reported that inflammatory activity did not influence LS [18].

Our study proved that TE, with or without other noninvasive fibrosis scores, is a valid method to monitor fibrosis and the effect of treatment, with considerable accuracy and reproducibility.

Magnetic resonance elastography and acoustic radiation force impulse (ARFI) elastography are alternative new valid noninvasive strategies for assessing hepatic fibrosis in chronic hepatitis [19].

Recently, some studies have reported the diagnostic accuracy of ARFI elastography for liver fibrosis in patients who achieved an SVR following antiviral therapies and its ability to evaluate regression of liver fibrosis serially after the eradication of HCV infection [20].

However, further research is needed to evaluate the effectiveness of TE with other noninvasive imaging modalities such as ARFI and magnetic resonance elastography for diagnosing liver fibrosis in patients with SVR to better characterize the early changes in liver tissue after successful DAAs treatment. LS measurement might potentially be useful for the dynamic assessment of the regression of cirrhosis after successful antiviral therapy and for stratification of the risk of complications such as HCC and mortality [21].

Conclusion

Our result showed a significant improvement in LS measurement in cirrhotic patients, but they still had cirrhosis, with lower LS values than the pretreatment values. This supports the fact that early diagnosis and treatment before advanced fibrosis and permanent liver damage is necessary to gain the maximum benefits from antiviral treatment [12].

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Conflicts of interest

Further study was required to evaluate regression of fibrosis in longer period. And to evaluate the biochemical changes also.

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