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Changes in liver stiffness measurements and fibrosis scores following sofosbuvir based treatment regimens without interferon

Aisha Elsharkawy,* Shereen Abdel Alem,* Rabab Fouad,* Maissa El Raziky,* Wafaa El Akel,* Mahmoud Abdo,* Omnia Tantawi,* Mohamed AbdAllah,† Marc Bourliere‡ and Gamal Esmat*

*Endemic Medicine and Hepatology Department, Faculty of medicine, Cairo University, Cairo, †Medical Research Division, National Research Centre, Giza, Egypt; and ‡Department of Hepato-Gastroenterology, Hospital Saint Joseph, Marseille, France

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Correspondence
Shereen Abdel Alem, Faculty of Medicine, Cairo University, Cairo, Egypt, post code11562.
Email: shery_2424@yahoo.com

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Abstract

Background and Aim: Accurate evaluation of the degree of liver fibrosis in patients with chronic liver diseases is crucial, as liver fibrosis is important in order to make therapeutic decisions, determine prognosis of liver disease and to follow-up disease progression. Multiple non-invasive methods have been used successfully in the prediction of fibrosis; however, early changes in non-invasive biomarkers of hepatic fibrosis under effective antiviral therapy are widely unknown. The aim of this study is to evaluate changes of transient elastography values as well as FIB-4 and AST to platelet ratio index (APRI) in patients treated with Sofosbuvir-based treatment regimen.

Methods: This is a retrospective study including 337 chronic HCV Egyptian patients with genotype 4 mainly. They were treated with Sofosbuvir-based treatment regimen. Transient elastography values were recorded as well as FIB-4 and APRI were calculated at baseline and SVR12.

Results: There was a significant improvement of platelets counts, ALT and AST levels, which in turn cause significant improvement in FIB-4 and APRI scores at SVR12. Liver stiffness measurements were significantly lower in SVR12 (14.8 ± 10.7 *vs* 11.8 ± 8.8 kPa, $P = 0.000$). About 77% of responders and 81.1% of cirrhotic patients showed improvement in liver stiffness measurements at SVR12.Univariate and multivariate regression analysis showed that failure to achieve improvement in liver stiffness measurements were significantly associated with relapsers and low baseline liver stiffness measurement.

Conclusion: Sofosbuvir-based treatment resulted in a clinically significant improvement in parameters of liver fibrosis.

Introduction

Hepatitis C virus infection is one of the main causes of chronic liver disease worldwide.[1] The number of chronically infected persons worldwide is estimated to be about 180 million, but most are unaware of their infection.[2]

In recent years, the treatment of HCV has been evolved with the development of direct-acting antiviral (DAAs) therapies, and they have entered the clinical practice in 2014/2015. They showed a promising future for HCV treatment with higher SVR rates, shortened and simplified regimens, and minimal treatment-related side effects in HCV patients.[3]

Regression of liver fibrosis has been a main topic of research and discussion in the community of liver experts for decades. However, recent data have demonstrated the occurrence of fibrosis regression in a wide spectrum of chronic liver diseases including chronic viral hepatitis.[4]

Several studies reported that regression of liver fibrosis by using potent antiviral agents in CHC patients could be achieved by improving hepatic necroinflammation and alleviating damage in sustained responders and by slowing the progression in relapsers.[5–7]

Nowadays, transient elastography (TE) is a validated non-invasive method for assessing hepatic fibrosis in HCV patients with the advantages of considerable accuracy and reproducibility.[4] Furthermore, the utility of TE has been evaluated in monitoring progression of fibrosis in the setting of HCV recurrence after liver transplantation.[8] Previously, changes in liver stiffness (LS) both during and after IFN-based regimens have been examined by several studies.[9,10]

Several non-invasive laboratory methods such as FIB-4 and APRI have been demonstrated to be accurate in staging chronic liver diseases before antiviral treatment and prediction of hepatic fibrosis in HCV patients.[11–13] Moreover, they have been used to longitudinally follow patients with chronic hepatitis and to assess the effect of antiviral treatment.[14]

The aim of the present study was to evaluate the impact of Sofosbuvir-based treatment regimens on the changes of LS

measurements and non-invasive fibrosis scores using FIB-4 as well as APRI.

Methods

Patient population. This is a retrospective study including 337 chronic hepatitis C (CHC) patients with genotype 4 mainly recruited from Kasr Al-Aini Viral Hepatitis Center, Cairo University. All eligible patients were included according to inclusion criteria approved by the National Committee for Control of Viral Hepatitis: Age 18–75 years, HCV RNA positivity, any BMI (weight in kilograms/squared height in meters), Treatment-naïve or treatment experienced and any stage of fibrosis. Patients were excluded if they had HBV co-infection, HIV, decompensated liver cirrhosis, inadequately controlled diabetes mellitus (HbA1c >9%), HCC and extra-hepatic malignancy.

Liver cirrhosis was diagnosed on clinical basis involving laboratory tests and ultrasonographic findings of liver cirrhosis and/or LS measurement ≥12.5 kPa.[15]

Patients were subjected to history taking, clinical examination and routine laboratory work up. All patients underwent TE within 2 weeks before treatment initiation as well as FIB-4 and APRI were calculated.

All patients were treated with Sofosbuvir-based treatment regimens according to the approved treatment recommendation (EASL 2014)[16] and protocol approved by the National Committee for Control of Viral Hepatitis in Egypt. These regimens included sofosbuvir/simeprevir, sofosbuvir/ribavirin, and sofosbuvir/daclatasvir with or without ribavirin. Patients were assessed for HCV RNA at week zero (baseline), EOT (End of treatment) and 12 weeks after EOT (SVR12). Undetectable HCV RNA by quantitative polymerase chain reaction assay (Cobas Amplicor, HCV Roche, Branchburg, NJ, USA, v 2.0, detection limit 15 IU/mL) 12 weeks after EOT was defined as SVR12, which is widely accepted and recognized as indicative of therapeutic success.[16]

The study was conducted according to the principles of the Declaration of Helsinki and was approved by Institutional Review Board of faculty of medicine, Cairo University (N-38-2016). Written informed consent was obtained from each patient before receiving treatment.

Laboratory tests and calculated scores. Blood samples were collected and laboratory tests in the form of complete blood cell counts, liver, and kidney function tests in addition to HCV RNA by PCR were done. HCV RNA by PCR was done again at EOT and SVR12.Aspartate aminotransferase-to-platelet ratio index (APRI) and FIB-4 score were calculated at baseline and SVR12 according to the following equations:

- Aspartate aminotransferase-to-platelet ratio index score was calculated using Wai's formula[17]:

(AST/upper limit of normal)/platelet count (expressed as platelets $\times 10^9$ /L) × 100.

- FIB-4 score was calculated using Sterling's formula[18]:

Age (y) × AST (IU/L) /platelet count ($\times 10^9$/L) × $\sqrt{}$ALT (IU/L)).

Aspartate aminotransferase-to-platelet ratio index cut-off greater than 1.0 predict cirrhosis while cut-off greater than 0.7 predict significant hepatic fibrosis,[19,20] but FIB-4 cut-off > 3.25 had positive predictive value of 65% for advanced fibrosis and cut-off < 1.45 had negative predictive value of 90% for advanced fibrosis and cirrhosis.[18]

Ultrasound transient elastography. Liver stiffness measurements were done for all patients with TE (Echosens, Fibroscan 502, Paris, France). At least 10 valid measurements were performed and median of LS expressed in kilopascals (kPa) was reported.[21] Only examinations with success rate > 60% and interquartile range (IQR) < 30% were included and considered reliable. At baseline, all patients (337) did ultrasound TE examination but 12 weeks after EOT, only 328 patients did the examination. TE results were correlated to different stages of liver fibrosis according to the histological staging system of METAVIR. The used cut-off values were as follows[15,22]:

- < 7.1 kPa = non-significant fibrosis <F2.
- From ≥ 7.1 kPa to < 9.5 kPa = significant fibrosis (≥ F2).
- ≥ 9.5 kPa for advanced fibrosis (≥ F3) and ≥ 12.5 kPa for cirrhosis (F4)

Statistical analysis. All patients' data were tabulated and processed using SPSS version 10.0 for Windows XP (SPSS, Chicago, IL, USA). The quantitative data were described as mean, standard deviation or range and compared by Student's t-test. Stepwise multiple linear regression analysis was used to determine which baseline variables were associated with improvement in LS measurement. The general linear model was used to examine the changes of TE values in KPa between baseline and SVR12. A value of $P < 0.05$ was considered as statistically significant.

Results

The Demographic criteria of the studied patients showed a mean age of 50.8 ± 11.3 years with male predominance (64.4%). About 56.1% were non-cirrhotic, and 52.2% were Treatment-naïve. Regarding LS measurement, 29.1% had non-significant fibrosis (< 7.1 kPa) (< F2), 17.2% had mild to significant fibrosis (≥ 7.1 to < 9.5 kPa) (≥ F2 to < F3), 8.6% had advanced fibrosis (≥ 9.5 kPa) (≥ F3) and 45.1% of studied population had cirrhosis (≥ 12.5 kPa) (F4). The mean value of FIB-4 score was 2.66 ± 2.22 while the mean value of APRI was 1.03 ± 0.54. At EOT, all patients were responders while 12 weeks after EOT, 310 (92%) patients achieved SVR while 27 (8%) patients were relapsers as shown in Table 1.

All patients whether cirrhotic or not showed statistically significant decline in ALT, AST, LS measurement, FIB-4 and APRI with significant improvement in platelets count in cirrhotic patients from baseline to SVR12 as shown in Table 2.

Significant decline was observed in ALT, AST, LS measurement, FIB-4 and APRI values between baseline and SVR12 among naïve patients and those who previously received antiviral therapy (Treatment experienced) as shown in Table 2.

Table 1 Demographic data in studied group

	(Mean ± *SD*, *n* %)
Demographics	
Age (years)	50.8 ± 11.3
Sex, *n* (%)	
Male	217 (64.4)
Female	120 (35.6)
Treatment status, *n* (%)	
Treatment Naïve.	176 (52.2)
Prior Peg/RBV treatment failures.	161 (47.8)
Presence or absence of baseline cirrhosis, *n* (%)	
Non-cirrhotic	189 (56.1)
Cirrhotic.	148 (43.9)
Baseline Liver stiffness values in kPa, *n* (%)	
< 7.1 kPa	98 (29.1)
≥ 7.1 kPa	58 (17.1)
≥ 9.5 kPa	29 (8.6)
≥ 12.5 kPa	152 (45.1)
Baseline FIB-4, *n* (%)	
< 1.45	104 (30.9)
1.45 – 3.25	144 (42.7)
> 3.25	89 (26.4)
Baseline APRI, *n* (%)	
< 1	233 (69.1)
> 1	104 (30.9)
Baseline Liver stiffness measurement (kpa)	14.63 ± 10.68
Baseline FIB-4	2.66 ± 2.22
Baseline APRI	1.03 ± 0.54
Response at 12 weeks after EOT (SVR12), *n* (%)	
Sustained responders	310 (92)
Relapsers	27 (8)

Among responders, a significant decline in platelets, ALT, AST, LS measurement, FIB-4 and APRI values was observed at SVR 12 ($P = 0.000$) Table 3.

Decreased LS measurements from baseline to SVR12 was observed through all fibrosis stages, but it was more obvious among patients with higher baseline LS values ≥ 12.5 as shown in Figure 1.

Improvement of LS measurements was not associated with response to Sofosbuvir based therapy or history of previously receiving antiviral therapy $P = 0.24$ and 0.26 respectively. However, 81.1% of cirrhotic patients showed improvement in their LS measurements with $P = 0.03$ as shown in Table 4.

Univariate and multivariate logistic regression analysis were done in which failure to achieve improvement in LS measurement is the dependent factor. Being a relapser or having lower baseline LS values were significant predictors of non-improvement in LS measurement ($P = 0.01$ and < 0.01 respectively) with odd ratio (OR: 3.2 and 0.33, respectively) as shown in Table 5.

Discussion

The Ministry of Health in Egypt have been successfully introduced DAAs regimens as a part of a national treatment program for CHC patients in the second half of 2014 where all eligible patients were treated with DAAs according to the approved treatment recommendation (EASL 2014).[16]

Higher rates of SVR and improvement of liver fibrosis are the major goals for CHC treatment with DAAs. The achievement of SVR results in resolution of liver fibrosis[23,24] that in turn reduces risk of liver related complications such as hepatic decompensation, variceal bleeding and HCC.[25,26] The current anti-HCV therapies were not designed to be anti-fibrotic but are focused on virus eradication, as HCV is a composite indicator of liver fibrosis and a

Table 2 Changes of Laboratory tests and non-invasive fibrosis markers among different groups at baseline and SVR12

		Presence or absence of baseline cirrhosis		Treatment status	
		Non-cirrhotic	Cirrhotic	Treatment-Naïve	Treatment Experienced
Number of patients (*n*; %)		189 (56.1)	148(43.9)	176 (52.2)	161(47.8)
Laboratory tests:					
PLT (10^3/mm^3)	Baseline (Mean ± *SD*)	225.2 ± 63.8	142.2 ± 56.4	189.5 ± 76.6	185.6 ± 69.3
	SVR12 (Mean ± *SD*)	221.2 ± 62.6	233.7 ± 218	228.7 ± 145	224.5 ± 163.4
	P value	0.3	< 0.01	0.01	0.03
ALT (U/L)	Baseline (Mean ± *SD*)	53.5 ± 35	84.4 ± 52	68.4 ± 46.9	66.3 ± 46
	SVR12 (Mean ± *SD*)	19.8 ± 8.5	30.4 ± 28	21.3 ± 12.9	28.5 ± 26.1
	P value	< 0.01	< 0.01	< 0.01	< 0.01
AST (U/L)	Baseline (Mean ± *SD*)	46.6 ± 27.8	81.3 ± 42.1	64 ± 40.2	60.1 ± 37.6
	SVR12 (Mean ± *SD*)	23.7 ± 12.1	35.9 ± 27.3	27.3 ± 20.4	31.4 ± 22.1
	P value	< 0.01	< 0.01	< 0.01	< 0.01
Non-invasive fibrosis markers:					
Liver stiffness measurement (Kpa)	Baseline (Mean ± *SD*)	7.7 ± 3.21	23.5 ± 10.3	13.9 ± 9.6	16 ± 11.8
	SVR12 (Mean ± *SD*)	6.5 ± 2.8	18.1 ± 9.5	11.5 ± 8.6	12 ± 9.1
	P value	< 0.01	< 0.01	< 0.01	< 0.01
FIB-4	Baseline (Mean ± *SD*)	1.7 ± 0.97	3.92 ± 2.7	2.72 ± 2.61	2.6 ± 1.7
	SVR12 (Mean ± *SD*)	1.3 ± 0.91	2.81 ± 1.91	2 ± 1.9	2 ± 1.3
	P value	< 0.01	< 0.01	< 0.01	< 0.01
APRI	Baseline (Mean ± *SD*)	0.6 ± 0.47	1.7 ± 1.4	1.1 ± 1.2	0.99 ± 1.02
	SVR12 (Mean ± *SD*)	0.35 ± 0.24	0.8 ± 0.71	0.5 ± 0.6	0.53 ± 0.44
	P value	< 0.01	< 0.01	< 0.01	< 0.01

Table 3 Changes of Laboratory tests and non-invasive fibrosis markers according to response of treatment in total studied patients, sustained responders and relapsers at baseline and SVR12

		Total studied patients	Sustained responders	Relapsers
Number of patients (*n*; %)		337 (100%)	310 (92%)	27 (8%)
Laboratory tests:				
PLT (10^3/mm^3)	Baseline (Mean ± *SD*)	187.8 ± 73.2	193 ± 72.5	133.2 ± 58.2
	SVR12 (Mean ± *SD*)	226.9 ± 153.3	215.7 ± 127.7	341.1 ± 296.1
	P value	0.001	0.02	0.01
ALT (U/L)	Baseline (Mean ± *SD*)	67.5 ± 46	66.3 ± 46.5	79.8 ± 39.7
	SVR12 (Mean ± *SD*)	24.6 ± 20.3	21.5 ± 10.5	56.4 ± 50.6
	P value	0.000	0.000	0.11
AST (U/L)	Baseline (Mean ± *SD*)	62.3 ± 39	60.2 ± 38.3	83.2 ± 40.5
	SVR12 (Mean ± *SD*)	29.2 ± 21.3	26 ± 12.5	61.5 ± 49.7
	P value	0.000	0.000	0.06
Non-invasive fibrosis markers:				
Liver stiffness measurement (Kpa)	Baseline (Mean ± *SD*)	14.8 ± 10.7	14 ± 10	26.2 ± 13
	SVR12 (Mean ± *SD*)	11.8 ± 8.8	10.8 ± 8	23.7 ± 10.5
	P value	0.000	0.000	0.16
FIB-4	Baseline (Mean ± *SD*)	2.7 ± 2.2	2.5 ± 1.93	4.72 ± 3.81
	SVR12 (Mean ± *SD*)	2 ± 1.6	1.81 ± 1.32	3.84 ± 2.98
	P value	0.000	0.000	0.07
APRI	Baseline (Mean ± *SD*)	1.03 ± 1.1	0.97 ± 1.1	1.8 ± 1.3
	SVR12 (Mean ± *SD*)	0.53 ± 0.54	0.5 ± 0.4	1.4 ± 1.24
	P value	0.000	0.000	0.09

causative agent of liver injury and inflammation.[27,28] Liver fibrosis remains even after HCV eradication despite its gradual resolution after SVR; the accurate and serial estimation of liver fibrosis is desirable.

Our study is among the first studies evaluating the impact of Sofosbuvir-based regimens without IFN on the changes of LS measurement by TE and liver fibrosis scores as determined by FIB-4 and APRI.

Similar to Bachofner *et al.*, 2016 study, our study reported a significant decline 12 weeks after EOT for LS measurements and validated fibrosis scores as FIB-4 and APRI. These scores are affected by the reduction of AST, ALT, and platelets levels denoting significant improvement of liver fibrosis (platelets) and necroinflammation (AST and ALT) following Sofosbuvir treatment. Also, Sustained responders showed significant reduction in these scores while reduction of these scores in relapsers was not significant.[29]

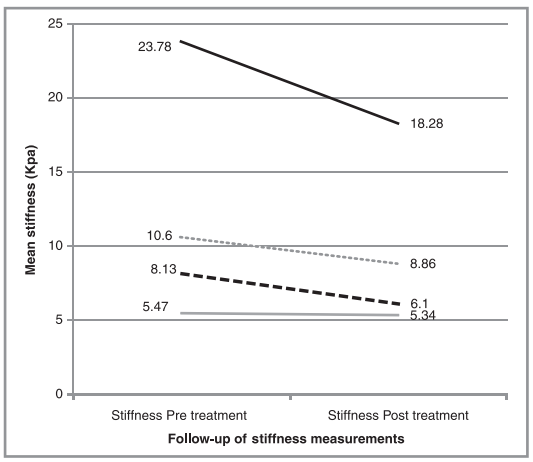

Figure 1 The mean liver stiffness values at baseline and SVR12 in the four groups of studied patients classified according to their baseline liver stiffness values. <7.1; =>7.1; =>9.5; =>12.5

Liver biopsy is the gold standard for assessing liver fibrosis regression following DAAs treatment, but it is no longer accepted by large number of patients because of invasiveness and higher rate of complications especially with the recent advances in HCV treatment,[30,31] it is difficult and impractical to perform serial liver biopsies for monitoring the dynamic changes in liver fibrosis after the achievement of SVR. Therefore, assessment of liver fibrosis by liver biopsy is gradually replaced by non-invasive and safe methods and they are currently being used in clinical practice.[32]

Transient elastography can be used to monitor potential regression of liver fibrosis after IFN treatment and may predict the treatment outcome of CHC as demonstrated in several clinical studies.[33–35] However, few studies have explored the role of TE in detecting dynamics of liver fibrosis and changes in LS in CHC patients who achieved SVR following DAAs therapies.[27,29,36]

Improvement of LS measurements occur early after therapy (12 weeks after EOT) regardless treatment outcome (77% of sustained responders and 63% of relapsers) because the temporary reduction in viral replication may be sufficient to lower LS measurement. This early reduction in LS measurement following DAAs treatment remains questionable as this reduction represents an actual improvement in liver fibrosis or as a result of reduction in liver inflammation because of antiviral treatment however the influence of inflammation on the LS assessment is controversial. Some studies suggested that LS increased with increasing necroinflammatory activity of liver[9,37] and the resolution of this necroinflammatory activity correlated with

Table 4 Liver stiffness improvement among different groups

	Improvement	No improvement	*P* value
Response, *n* (%)			
Responder	235 (77)	69 (23)	0.24
Relapsers	15 (63)	9 (37)	
Treatment status, *n* (%)			
Treatment-naïve	126 (73.7)	45 (26.3)	0.26
Treatment experienced	124 (79)	33 (21)	
Presence or absence of baseline cirrhosis, *n* (%)			
Non-cirrhotic	129 (71.7)	51 (28.3)	0.03
Cirrhotic	121 (81.8)	27 (18.2)	

Table 5 shows univariate and multivariate regression analysis in which failure to achieve improvement in liver stiffness measurement is the dependent factor

	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Male gender	0.70	0.40–1.2	0.22	0.69	0.40–1.2	0.18
Age	0.01	0.97–1.0	0.59	—	—	—
Elevated ALT (above ULN 40)	0.82	0.42–1.5	0.54	—	—	—
Elevated AST (above ULN 40)	1.8	0.89–3.7	0.10	1.6	0.86–3.1	0.14
Low platelets ($< 150 \times 10^3/mm^3$)	1.7	0.85–3.5	0.13	1.7	0.86–3.5	0.13
Relapsers	3.2	1.24–8.4	0.01	3.4	1.3–8.7	0.01
Low Baseline Liver stiffness values	0.33	0.21–0.53	<0.01	0.3	0.20–0.50	<0.01

transaminases which normalize following antiviral therapy while other studies reported that inflammatory activity did not influence LS.[15,34]

Magnetic resonance elastography (MRE) and acoustic radiation force impulse (ARFI) elastography are other validated non-invasive methods for assessing hepatic fibrosis in chronic viral hepatitis.[38,39] Recently, A few studies have reported the diagnostic accuracy of ARFI elastography for liver fibrosis in patients who achieved SVR following antiviral therapies and its ability to evaluate regression of liver fibrosis serially after the eradication of HVC.[40,41] Therefore, further researches are needed to evaluate the effectiveness of TE with other non-invasive imaging modalities as ARFI and magnetic resonance elastography (MRE) for diagnosing liver fibrosis in patients with SVR in order to better characterize the early changes in liver tissue after successful DAAs treatment.

Liver stiffness measurement might have the potential for dynamically assessing the regression of cirrhosis after successful antiviral therapy and stratify the risk of complications such as HCC and mortality.[42,43] Our result showed significant improvement in LS measurement in 81.1% of cirrhotic patients, but they remain to have cirrhosis with lower LS values than pretreatment values. Chekuri *et al.* (2016) reported a significant reduction in LS values among cirrhotic patients, but 60% who were cirrhotic pretreatment remained cirrhotic at SVR24.[27] Cirrhosis persists in patients who achieved SVR.[44,45]

All these results are supporting the fact that early diagnosis and treatment before advanced fibrosis and permanent liver damage is necessary to have the maximum benefits from antiviral treatment.

With the previously used Pegylated interferon and ribavirin, several studies reported factors associated with decline in LS measurements after antiviral therapy as baseline fibrosis stage, baseline activity, SVR, BMI, age, and viral load.[5,10] With the recent use of DAAs, this issue is still under research, however it seems that age, viral load, BMI, and baseline activity will no longer have a role.

In conclusion, Sofosbuvir-based therapy causes a clinically significant improvement in hepatic fibrosis measures using TE as well as FIB4 and APRI even in cirrhotic patients, but earlier treatment is urgent before permanent liver damage has occurred. Longer follow-up is recommended to fully understand the impact of SVR on dynamics of liver fibrosis and regression.

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