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Research Article

Non-Invasive Fibrosis Scores and Liver Stiffness Changes in Chronic Hepatitis C after Sofosbuvir-based Treatment -

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ABSTRACT

Background: The precise evaluation of hepatic fibrosis is crucial in the management of Chronic Hepatitis C (CHC). Multiple non-invasive serological scores and devices have been used in the accurate prediction of fibrosis however; early changes in non-invasive biomarkers of liver fibrosis following antiviral therapy are widely unknown. We aim to evaluate changes of liver stiffness and 6 non-invasive serological fibrosis scores, easy to calculate particularly in poor areas, following sofosbuvir- based treatment.

Methods: This is a cohort study that included 155 CHC Egyptian patients. Transient elastography values were recorded as well as Aspartate Aminotransferase-To-Platelet Ratio Index (APRI), FIB-4, Lok score, fibrosis index, King Score and fibro Q score were calculated at baseline and 12 weeks post-treatment.

Results: There was a significant decline of aminotransferases and hemoglobin levels in all patients. There was a significant improvement in all studied fibrosis scores 12 weeks post-treatment except the fibrosis index. Liver stiffness measurements were significantly lower 12-weeks post-treatment (10 ± 8.06 vs 9.27 ± 8.51 kPa, P-value = 0.001). 145 (93.6%) patients achieved sustained virological response. There was no difference between responders and non-responders in baseline or post treatment liver stiffness or fibrosis scores values.

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

Keywords: Fibrosis scores; Liver stiffness; Non-invasive fibrosis assessment; Chronic hepatitis C; Sofosbuvir-based treatment

INTRODUCTION

Hepatitis C Virus (HCV) is a worldwide aetiology of chronic hepatic insult particularly in Egypt where the main genotype is genotype 4 which is responsible for over 90% of infections, and the remaining is due to genotype-1 [1,2]. Chronic Hepatitis C (CHC) infection leads to progressive liver fibrosis, end-stage liver disease then hepatocellular carcinoma (HCC). Successful treatment leading to a Sustained Virologic Response (SVR) has been associated with a reduction of risk of all-cause mortality [3]. The development of Direct-Acting Antiviral (DAAs) therapies showed a promising future for HCV treatment with higher response rates, shortened and simplified treatment regimens and reduced treatment-related side effects [4].

Liver fibrosis regression has been a main topic of research for decades. Previous studies reported that regression of liver fibrosis in CHC patients is possible with the usage of potent antiviral agents through improving hepatic necro-inflammation and alleviating damage in patients with SVR. This regression of fibrosis leads to a reduced risk of liver-related complications such as decompensation and variceal bleeding [5-7]. Liver Stiffness Measurement (LSM) using Fibroscan allowed non-invasive staging of liver fibrosis and cirrhosis with proven clinical accuracy [8]. Previously, differences in liver stiffness measurements during and after interferon–based regimens were examined by several studies [9,10].

Several non-invasive serological markers have been also reported to predict the presence of significant fibrosis and/or cirrhosis in CHC patients with adequate accuracy. Some of these markers are based on routine laboratory data that are readily available in most hospital files [11-13]. In addition, they have been used to longitudinally follow patients with CHC and to assess the effect of antiviral therapy [14]. Transient elastography or serum biomarkers, are proved to be adequate for diagnosis of severe fibrosis/cirrhosis patients with HCV or HIV-HCV co-infection. They also can be used to prioritize patients for CHC treatment based on the stage of the disease [15]. The aim of the present study was to evaluate the changes of liver stiffness measurements and non-invasive fibrosis scores following Sofosbuvir-based treatment regimens in Egyptian patients with CHC.

PATIENTS AND METHODS

This is a cohort study that recruited 155 Egyptian patients with chronic hepatitis C who were collected and followed up in the period between February 2015 and October 2016. All patients were candidates for anti-viral therapy according to the guidelines of the National Committee for Control of Viral Hepatitis (NCCVH). The patients were recruited from the National Hepatology & Tropical Medicine Research Institute (NHTMRI) and Kasr Al-Aini Viral Hepatitis Center (KAVHC), Faculty of Medicine, Cairo University. Treatment regimens included: Sofosbuvir and daclatasvir ± weight-based ribavirin (RBV), sofosbuvir and simeprevir, sofosbuvir and weight-based RBV plus weekly PEGylated interferon (Peg IFN) for 12 weeks. The study was approved by the Ethical Committee for the National Control of Viral Hepatitis of the Ministry of Health. A written informed consent was obtained from all patients. The study was performed in compliance with the ethics principles of the 1975 Declaration of Helsinki and its later amendments with Good Clinical Practice (GCP) guidelines.

Patients were included according to the inclusion criteria approved by NCCVH: patients with chronic HCV infection proven by positive HCV PCR, age 18-75 years, any Body Mass Index (BMI) (weight in kilograms/squared height in meters), Treatment-naive or treatment experienced, any stage of liver fibrosis and patients practicing adequate contraception. Exclusion criteria include: other causes of chronic liver disease e.g. Hepatitis B virus (HBV) or HIV -coinfection, hemochromatosis, alpha 1-antitrypsin deficiency, Wilson disease, autoimmune disease and alcoholic liver disease, HCC and extra-hepatic malignancy.

Participants were subjected to: Full history taking and clinical examination. Routine laboratory investigations including: Complete blood picture, International Normalized Ratio (INR), total serum bilirubin, Alanine Transaminase (ALT), Aspartate Transaminase (AST) and Alfa Fetoprotein (AFP), before start of treatment and at end of treatment. Serum cholesterol and triglyceride, ANA & Thyroid-Stimulating Hormone (TSH) before start of treatment only. Quantitative Polymerase Chain Reaction (PCR) for HCV RNA (Cobas Amplicor, HCV Roche, Branchburg, NJ, USA, v 2.0, detection limit 15 IU/mL), before start of treatment, at end and 12 weeks followed treatment, Electrocardiography (ECG), abdominal ultrasound. Liver biopsy was not done to all participants as it is no more included in the

NCCVH guidelines for treatment of hepatitis C and it was replaced by fibroscan.

Calculated fibrosis scores

- **Aspartate aminotransferase-to-platelet ratio index (APRI):** was calculated using Wai's formula = (AST/upper limit of normal)/platelet count (expressed as platelets × 109/L) × 100 [16]
- **FIB-4 score** was calculated using Sterling's formula = [age (years) x AST (IU/L)]/[platelet count(109/L) x ALT (IU/L)1/2] [17]
- **Lok Score:** log odds = - 5.56 – 0.0089 x platelet count (103/mm3) + 1.26 x (AST/ALT) + 5.27 x INR [18].
- **Fibrosis index (FI score):** 8 - 0.01 × number of platelets (10^9/L) - albumin (g/dL) [19].
- **King score:** age (years) × AST (U/L) × INR/number of platelets (10^9/L) [20]
- **Fibro Q:** [(10 × age (years) × AST × PT INR)/ (PLT × ALT)] [21]

Transient Elastography (TE)

Liver stiffness was recorded to all patients before treatment and 12 weeks after the end of treatment. The clinical and laboratory data were collected at the time of transient elastography. The fibroscan (Echo sense Version 13 - 05/2009; software version 1.40, Paris) machine was performed at Endemic Medicine Department, Faculty of Medicine, Cairo University by a competent operator while blinded to the patients' clinical and laboratory data. Patients were fasting for a minimum of 6 h prior to TE.

LSM were taken in the right lobe of the liver in between the 9th to 11th intercostal spaces. Results were regarded as valid when: A number of 10 valid shots. A success rate (the ratio of valid readings to the total number of readings) above 60%. An interquartile range (IQR, reflecting the variability of LSM) <30% of the median LSM. The median value of LSM is expressed in kilopascal (kpa). Cut off values for liver stiffness measurements in Kpa in relation to Metavir score used during this study were according to de Ledinghen and Vergniol [22]. Patients were divided according to their LSM: non-significant fibrosis (< F2): 0-8.7 Kpa, significant fibrosis (≥F2-<F4): 8.8-14.4 Kpa. And Cirrhosis (F4): ≥14.5 Kpa. Patients with cirrhosis were also screened for esophageal varices.

Statistical methods

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 23. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparison of serial measurements (before and after) within each patient the non-parametric Wilcoxon signed rank test was used [23]. Correlations between quantitative variables were done using Spearman correlation coefficient [24]. P-values less than 0.05 were considered as statistically significant. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of steatosis for detection of responders.

RESULTS

This study included 155 Egyptian patients with chronic hepatitis C who completed the 3 months post treatment follow up period. They received sofosbuvir based treatment regimen if the form of: 82 patients: received Sofosbuvir 400 mg/day and daclatasvir 60 mg/day ± weight-based RBV (1000 mg [below 75 kg] to 1200 mg [above 75 mg]) for 12 weeks. Forty-two patients received Sofosbuvir 400 mg/d and simeprevir 150 mg/d for 12 weeks. Thirty-one patients received Sofosbuvir (400 mg) and weight-based RBV (1000 mg [below 75 kg] to 1200 mg [above 75 mg]) plus weekly Peg IFN for 12 weeks.

Demographic and laboratory features of the studied patients are shown in tables 1 and 2. The mean age of the studied patients was 45.78 ± 11.6 years with female predominance (60.6%). 81.9% were non- cirrhotic and 88.4% were Treatment-naïve. AST, ALT and hemoglobin levels significantly decreased in all patients 12 months post treatment.

Liver stiffness measurements mean values were found to be significantly reduced post treatment in all patients (p-values = 0.001) (Tables 3) but when we studied the changes in the distribution of patients among fibrosis stages after treatment we found no significant difference in their distribution among the fibrosis stages (Table 4).

APRI, Fib-4, LOK score, King Score and Fibro Q score mean values significantly reduced in all patients 12 months post-treatment. Fibrosis index was the only score that was not affected by treatment (Tables 3). No statistically significant difference was noticed in serum albumin, bilirubin, INR, Alfa fetoprotein (AFP).

Table 1: Baseline characteristics of the studied patients.

Variant Number (%)	Total (N = 155)
Age (yrs.) mean ±SD	45.78 ± 11.6
Sex Females Male	 94 (60.6%) 61 (39.4%)
Naive	137 (88.4%)
Prior Peg/ RBV treatment failures	18 (11.6%)
Cirrhotic Non-cirrhotic	28 (18.1%) 127 (81.9%)
SVR12	145 (93.6 %)
Relapsers	10 (6.4%)

SD = Standard Deviation

Table 2: Demographic & laboratory features before treatment and 12 weeks post treatment of the studied patients.

Variant	Total		
	Mean ± SD		P value
	Pre-treatment	12 weeks post-treatment	
Hemoglobin (g/ dL)	13.19 ± 1.97	12.57±1.68	<0.001
TLC / cmm	6.1 ± 2.09	6.1 ± 1.9	0.733
Platelets / cmm	215129.03 ± 83109.67	212980.65 ± 79403.17	0.518
ALT (U/L)	43.24 ± 20.5	24.18 ± 13.91	<0.001
AST (U/L)	39.6 ± 19.14	26.7 ± 12.67	<0.001
Albumin (g/dL)	4.06 ± 0.5	4.11 ± 0.51	0.155
Bilirubin (mg/dL)	0.72 ± 0.29	0.75 ± 0.34	0.276
INR	1.07 ± 0.14	1.07 ± 0.11	0.422
AFP (IU/mL) IQR*	2.5 to 6.11	3.1 to 6.2	0.332

SD: Standard Deviation; TLC: Total Leucocytic count; AFP: Alfa fetoprotein
*IQR: Inter quartile (1st to 3rd quartile), Not statistically significant P value is > 0.05.

Patients who achieved SVR with negative HCV-PCR after 12 weeks (SVR12) were 145 (93.6%) patients while 10 (6.4%) patients were relapsers as shown in table 1. When we compared LSM and the studied fibrosis scores values between responders and relapsers, we found no statistically significant difference (Table 5).

DISCUSSION

The major goals for CHC treatment are achieving high rates of SVR and improving HCV-induced liver fibrosis. Direct acting antivirals (DAAs) does not have an anti-fibrotic effect but mainly concerned with viral eradication [25,26]. In spite of the gradual decrease in liver fibrosis after SVR, hepatic fibrosis is still present and its accurate and repeated estimation is required [14]. Repeated liver biopsies in HCV patients carry a significant risk of complications, thus non-invasive techniques are now frequently used to assess fibrosis stage before and after HCV therapy. Transient elastography has been validated for the non-invasive assessment of liver fibrosis in CHC [27,28]. The aim of the present study was to assess the changes in liver stiffness measurements by transient elastography and the changes in different serological fibrosis scores as determined by APRI, FIB-4, Lok score, fibrosis index, King Score and fibro Q score following HCV treatment with sofosbuvir based regimens.

Similar to Bachofner, et al. and Elsharkawy, et al. [14,29], our study revealed that liver stiffness measurements significantly declined 12 weeks following the end of antiviral therapy. In addition, there was a significant improvement in all studied fibrosis scores except the fibrosis index. These scores are affected by the reduction of AST, ALT denoting significant improvement of liver fibrosis and necro-inflammation (as reflected by AST and ALT) following Sofosbuvir treatment. The present study did not reveal a significant improvement in platelet count that Elsharkawy, et al. [14] reported in their cirrhotic patients. This may be explained by our different patients' distribution within the fibrosis stages as the majority of our patients did not have liver cirrhosis (81.9%). The fibrosis index did not show a significant change and this may be attributed to the presence of serum albumin within the score that did not show significant changes after treatment. The improvement in serum albumin level and consequently the synthetic function of the liver may require longer duration to improve as reported by Maruoka, et al. [30] who found that serum albumin level increased gradually over the first 2 years following combined interferon therapy then plateaued while ALT level decreased rapidly during the first 6 months of therapy

Table 3: Changes in liver stiffness measurements and fibrosis scores after sofosbuvir based treatment regimens.

Variable	Pre treatment	Post treatment	P value
Liver stiffness (Kpa)	10 ± 8.06	9.27 ± 8.51	0.001
APRI	0.58 ± 0.5	0.37 ± 0.28	<0.001
FiB4	1.67 ± 1.48	1.41 ± 1.07	0.005
Lok score	-.61 ± 1.24	-.29 ± 1.17	<0.001
Fibrosis index	3.72 ± 0.53	3.68 ± 0.53	0.202
King score	12.39 ± 13.74	7.87 ± 9.66	<0.001
Fibro Q score	2.92 ± 2.77	3.40 ± 3.22	<0.001

All data are presented as mean ± standard deviation
Not statistically significant P value is > 0.05.

The advantage of combining unrelated noninvasive methods for assessment of liver fibrosis, such as transient elastography and serum biomarkers, is more effective for detecting significant fibrosis than combining two serum biomarkers. In addition, transient elastography allows direct measurement of the liver structure [28,31].

Although Bachofner, et al., [29] raised an issue that the early improvements in LSMs and fibrosis scores 12 weeks after the end of treatment is not due to a true fibrosis regression but related to a reduction of inflammation and related interstitial oedema but when they followed these changes after 9 months they confirmed further reductions in LSM and fibrosis scores. So we assume that even if the early changes are related to necro-inflammation improvement with or without mild improvement in fibrosis, as the current study revealed a non-significant change in patients' distribution within the fibrosis stages, but the actual fibrosis will improve overtime after viral eradication.

The influence of HCV-induced necro-inflammatory process on LSM is controversial. Some studies suggested that LSM increases with enhanced necro-inflammatory activity of the liver [9,31] and the resolution of this necro-inflammatory activity following antiviral treatment correlated with AST and ALT which normalize following anti-viral therapy. Other studies revealed that inflammatory activity didn't affect LSM [31,32].

Transient elastography could be used to monitor potential regression of liver fibrosis after IFN treatment and may predict the treatment outcome of chronic hepatitis C as demonstrated in several clinical studies [33,34]. However, few studies have studied the role of fibroscan in detecting the dynamics of hepatic fibrosis and changes in LSM in SVR patients following DAAs treatment. [25,29,34].

In conclusion, sofosbuvir-based treatment regimens for CHC result in a rapid significant reduction in LSM as measured by transient elastography although we found no significant change in the distribution of patients among the fibrosis stages. There was a

Table 4: Liver fibrosis stage changes 12 months post-treatment of the studied groups.

Fibrosis stage N (%)	Total (N = 155)		Group 1 (N = 82)		Group 2 (N =42)		Group 3 (N = 31)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
< F2	95 (61.3)	111(71.6)	49 (59.7)	54 (65.9)	24 (57.1)	31 (73.8)	22 (71)	26 (83.9)
≥F2 - <F4	32 (20.6)	21 (13.6)	17 (20.8)	13 (15.8)	10 (23.9)	5 (11.9)	5 (16.1)	3 (9.6)
F4	28 (18.1)	23 (14.8)	16 (19.5)	15 (18.3)	8 (19)	6 (14.3)	4 (12.9)	2 (6.5)
P value	0.134		0.668		0.241		0.498	

*<F2: Non-significant fibrosis; ≥F2 - <F4: Significant fibrosis
Not statistically significant P value is > 0.05.

Table 5: Pre-treatment and post treatment changes in liver stiffness measurement and fibrosis scores values in responders and non-responders.

Fibrosis score	Responders	Non-responders	P-value
Pre-treatment			
Liver stiffness (Kpa)	10 ± 8.1	10.02 ± 7.38	0.928
APRI	0.58 ± 0.50	0.61 ± 0.5	0.995
FiB4	1.66 ± 1.49	2.08± 1.74	0.355
Lok score	-0.60 ± 1.24	-0.88 ± 1.58	0.710
Fibrosis index	3.72 ± 0.51	3.93 ± 1.12	0.191
King score	12.39 ± 13.85	12.30 ± 9.63	0.693
Fibro Q score	2.90 ± 2.79	3.66 ± 2.28	0.299
The changes in fibrosis scores			
APRI	0.21 ± 0.45	.14 ± 0.5	.410
FiB4	0.25 ± 1.13	.61 ± 1.24	.743
Lok score	-0.32 ± 1.12	-.14 ± 0.83	.550
Fibrosis index	0.04 ± 0.05	.11 ± 1.36	.491
King score	4.58 ± 11.43	2.11 ± 10.17	.343
Fibro Q score	0.21 ± 0.45	.14 ± 0.5	.410

Not statistically significant P value is > 0.05
SD: standard deviation.

significant improvement in all studied fibrosis scores 12 weeks post-treatment except the fibrosis index. These non-invasive fibrosis scores could be helpful in the developing regions of limited resources for patients follow up. The change in LSM values may not be explained by a regression in the actual fibrosis.

CONFLICT OF INTEREST

All included authors declare absence of any financial or personal relationships with other people or organizations that could inappropriately influence and bias the work.

SUBMISSION DECLARATION

This work has not been published previously, is not under consideration for publication elsewhere, its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out and, if accepted, will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

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