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Evaluation of liver stiffness by non-invasive methods after eradication of HCV by direct-acting antiviral therapy: a retrospective observational study

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Abstract

Background: There is some debate about the effect of direct-acting antiviral regimens (DAAs) on regression of liver fibrosis, but no definitive conclusion has been reached. The aim of this study is to evaluate liver stiffness measurement changes after attaining sustained virologic response (SVR) for HCV following DAAs treatment using non-invasive methods.

Methods: This retrospective study analyzed 84 patients with chronic HCV infection who were treated with DAAs and achieved SVR after treatment. At baseline and 24 weeks post sustained virologic response (SVR24), transient elastography values were obtained and the Fibrosis-4 score (FIB-4) and AST to Platelet Ratio Index (APRI) were calculated.

Results: Compared to baseline data, patients achieved SVR following DAAs treatment showed significant decrease in liver stiffness measurement at SVR24 (16.6±12.6 vs 12.6 ± 11.6 kPa) (P<0.01) with significant fibrosis down staging in the majority of patients. Furthermore, there was a significant improvement as regarding, FIB-4 and APRI scores at SVR24 (2.1±1.9 vs 5.1 ± 2.3 and 0.33 ± 0.2 vs 0.93 ± 0.4 respectively, P <0.001).

Conclusion: DAAs treatment significantly improved liver stiffness as measured by FibroScan. Further, multicenter prospective studies with histopathologic correlations are needed to clarify the impact of DAAs on the improvement of necroinflammation and fibrosis.

Introduction

Chronic hepatitis C virus (HCV) infection is a major cause of liver cirrhosis, fibrosis, and liver cancer [1]. The goals of HCV treatment are to achieve SVR, avoid liver injury and its repercussions, and reverse liver fibrosis.

In persistent infections, the level of liver fibrosis is a crucial component in the progression of liver disease. Effective HCV treatment decreases fibrosis and its associated effects [2-6].

Due to liver biopsy's invasive nature, many other non-invasive techniques have been established to assess the stage of liver fibrosis [7,8] like the Aminotransferase (AST)-to-Platelet Ratio Index (APRI) score [8], and the Fibrosis-4 (FIB-4) score is a validated alternative noninvasive serological biomarker for liver fibrosis [9].In addition, several other noninvasive parameters have been demonstrated to be accurate tools of liver fibrosis assessment. For instance, FibroTest (BioPredictive) can indicate the severity of liver disease, which can range from mild to severe [10, 11], FibroMeter (BioLiveScale) is an effective formula in the assessment of significant fibrosis and cirrhosis [12, 13]. In addition, numerous studies have validated HepaScore (Quest Diagnostics) [14-19] and have shown it to be superior to APRI and FibroTest in detecting cirrhosis [13, 20].

Transient elastography (TE) has recently become well-known as a non-invasive standard for the measurement of liver stiffness (LS) and is commonly utilized for liver fibrosis assessment with a high degree of precision in evaluating the severity of fibrosis and cirrhosis [21-23], with using controlled attenuation parameter (CAP) as it is noninvasive quantitative marker of hepatic steatosis[24, 25].

Previous studies showed that antiviral therapy improved liver histology by inducing reversal of liver damage in patients with SVR and also reducing the progression of relapsing patients [26, 27]. Recently, new treatments for hepatitis C viral infection were established with direct-acting agents (DAAs) that having a short duration of treatment (12 or 24 weeks) and extremely high success rates (> 90%) and very few side effects [28].

There is a paucity in studies evaluated the dynamic changes in liver stiffness measurements (LSMs) and the noninvasive index measures of chronic hepatitis C (CHC) patients treated with DAAs [29-31]. The aim of this study was to investigate the changes in LSM by using noninvasive

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methods such including TE, APRI score, and FIB-4 index after attaining SVR for HCV following DAA treatment.

Materials and methods

Patients

This retrospective observational study included 84 patients with chronic HCV infection who received DAAs from January 2018 to March 2021 in Specialized Medical Hospital, Mansura, Egypt.

Inclusion criteria: included, age >18 years, chronic hepatitis C infection (HCV antibody present for more than 6 months with a detected HCV viral load by quantitative PCR in the blood before treatment), completion of DAAs therapy by the patient with documented SVR24, and the availability of the results of FibroScan measurements before treatment and after achieving SVR24.

Exclusion criteria: liver disease caused by other etiologies, pregnancy and lactation, HIV co-infection, previous interferon-based therapy, decompensated liver cirrhosis (e.g., ascites or encephalopathy), previous or current hepatocellular carcinoma, extrahepatic malignancies, comorbid diseases (for example heart or renal failure), solid organ transplantation, and concurrent use of immunomodulatory agents.

Methods: The evaluation of every patient included a complete history and physical examination, as well as investigations, which include:

1. Laboratory: Liver biochemical tests (ALT-AST-bilirubin-GGT-albumin-alkaline phosphatase and INR), alpha-fetoprotein (AFP), HCV genotype assay, which was done utilizing the Abbott Real Time HCV Genotype II assay (Abbott Molecular, Abbott Park, IL, USA), kidney function tests (blood urea nitrogen and serum creatinine), complete blood count (CBC).

2. Radiological: Abdominal ultrasonography, triphasic multi-slice CT, and transient elastography.

Transient elastography (TE) and controlled attenuation parameter (CAP) were attained by means of the FibroScan device (FibroScan, Echosens, Paris, France) by a professional FibroScan operator and the median of liver stiffness (LS) expressed in kilopascals (kPa). For classification the following cut-off values were used (F0/F1/≤7 kPa; F2: moderated fibrosis ≥ 7.1 kPa; F3: advanced fibrosis ≥ 9.5 kPa; F4: cirrhosis ≥ 12.5 kPa) [32]. For scanning the right lobe of the liver, patients were supine with their right hands in a maximally abducted position. When at least 10 valid measures were acquired, 60 percent of the measurements were valid, and the interquartile range was less than 30 percent, these values were deemed legitimate, and their medians were utilized for analysis. The CAP is a probe-obtained ultrasonic attenuation measurement of the liver at 3.5 MHz. Validated CAP measurements employ the identical LS criteria and signals as LS measurements. Using Sterling's formula, the FIB-4 score was calculated [9, 33], and using Wai's formula [8], the APRI score was calculated. APRI cut-off greater than 1.0 predicts cirrhosis, while a cut-off greater than 0.7 predicts significant hepatic fibrosis.

Antiviral therapy: All participants received a 12- or 24-week course of DAAs regimens in accordance with the Egyptian national treatment protocol. DAAs were sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, elbasvir/grazoprevir for 12 or 24 weeks, either with or without ribavirin. As defined by the Polymerase Chain Reaction (PCR) assay, sustained virologic response (SVR) is undetectable serum HCV RNA at 24 weeks after end of therapy. Treatment choice was based on the decision of a local multidisciplinary conference of experienced clinicians. The study followed the guidelines of 1975 Declaration of Helsinki and approved by the local committee of ethics of the Mansoura University Hospital, and all patients signed written informed consent.

Statistical Analysis

Data were expressed as mean and standard deviation (SD) for numerical data, and as frequency and percentage for qualitative data. The student t-test or the non-parametric Mann–Whitney rank-sum test were used to analyze quantitative data, as appropriate. Categorical variables were analyzed by the Chi-square test. The differences between baseline and end of follow-up measurements were assessed by the Wilcoxon matched pairs signed-rank test. A decrease of 20% or more from baseline values in liver stiffness is considered an improvement. All statistical evaluations were performed with SPSS software (version 16.0, SPSS Inc, Chicago, IL).

Results. From January 2018 to March 2021, a total of 88 patients received DAAs for treatment of chronic HCV infection. Four patients were excluded; three patients didn't achieved SVR, and one lost his follow up. After 12 - 24 weeks of DAAs therapy; 84 (96.6%) patients had SVR (undetectable HCV viral load by quantitative PCR in the blood at least 24 weeks after the end of treatment). Baseline clinical and demographic data of these patients is shown in **Table 1**. The studied patients showed male predominance; 53 (61 %). Their age was 51.0±4.9 years. 15 (17.8%) patients were F0-F1, 18 (21.4%) patients were F2, and most of the patients were F3 and F4 (26.3 and 34.5% respectively), according to the estimated METAVIR score based on baseline LSM. For the liver stiffness evaluation parameters, the FIB 4 index was 5.1±2.3, the APRI was 0.93±0.4, baseline liver stiffness was 16.6±12.6, and the baseline CAP was 247.0±49.9.

Table 2 shows the clinical and demographic data of the patients before and after achieving SVR; there were no statistically significant differences in body mass index, creatinine, WBC, and hemoglobin in the studied patients before and after SVR. However, there was a statistically significant decrease (improvement) as regards total bilirubin, AST, ALT, INR, and alpha-fetoprotein in our patients after SVR compared to before SVR ($p < 0.001$) and a significant increase (improvement) in platelets and albumin in our patients after SVR compared to before SVR ($p < 0.01$).

Table 1. Characteristics of the patients who were involved in the study.

Parameter		Patients (No = 84)
Age in years		51.0±3.9
Gender	**Males**	53 (61 %)
	Females	31 (39 %)
Body mass index (kg/m2)		22.3 ±4.8
Smoking history		35 (41.66 %)
ALT (U/L)		96.75 ± 77.42
AST (U/L)		74.3±61.8
Albumin (gm/dl)		4.09 ± 0.41
Total bilirubin (g/dl)		0.69± 0.36
GGT (U/L)		86.46 ± 22.72
International normalization ratio (INR)		1.3±0.2
Creatinine (mg/dl)		0.6±0.2
WBC (×10^3/ml)		6.81±2.1
Platelets (× 10^9/L)		160.29 ±77.13
Hemoglobin (g/dl)		13.2±1.7
Baseline HCV RNA (log_{10} IU/ml)		7.27±0.9
Alpha-Fetoprotein (ng/ml)		7.4±16.1
Fibrosis stage	**F0-F1**	15 (17.8%)
	F2	18 (21.4%)
	F3	22 (26.3%)
	F4	29 (34.5%)
FIB 4 index		5.1±2.3
APRI score		0.93±0.4
Baseline liver stiffness (kPa)		16.6±12.6
Baseline CAP (dB/m)		247.0±49.9

APRI; *AST/platelet ratio index*, **ALT**; *alanine aminotransferase*, **GGT**; *γ-glutamyl transpeptidase*, **AST**; *aspartateaminotransferase*, **FIB-4 score**; *Fibrosis-4 index*, **HCV**;*hepatitis C virus*,**CAP**; *controlled attenuation parameter*, **WBC**; *white blood cells*, **SVR**; *sustained virologic response.*

Table 2: Demographic and clinical data of the patient's pre-treatment and after SVR

Variables	Pre-treatment	After SVR	p-value
Body mass index (kg/m2)	22.3 ±4.8	22.20 ±4.5	0.29
AST (U/L)	74.3±61.8	22.3±12.2	<0.001
ALT (U/L)	96.75 ± 77.42	21.3±10.1	<0.001
Total bilirubin (g/dl)	0.69± 0.36	0.43±0.32	<0.001
Albumin (gm/dl)	4.09 ± 0.41	4.45±0.29	<0.001
GGT (U/L)	86.46 ± 22.72	58.8±11.5	<0.001
international normalization ratio (INR)	1.3±0.2	1.0±0.19	<0.001
creatinine (mg/dl)	0.6±0.2	0.8±0.3	0.033
WBC (×10^3/ml)	6.81±2.1	6.77±1.1	0.34
Hemoglobin (g/dl)	13.2±1.7	13.5±1.3	0.31
Platelets (×10^9/L)	160.29 ±77.13	186.59 ±69.19	<0.001
Alpha-Fetoprotein (ng/ml)	7.4±16.1	3.9±113	<0.001

Table 3: The noninvasive parameters of fibrosis of the patients pre-treatment and after SVR

Variables	Pre-treatment	After SVR	p-value
FIB4 index	5.1±2.3	2.1±1.9	<0.001
APRI	0.93±0.4	0.33±0.2	<0.001
liver stiffness (kPa)	16.6±12.6	12.6±11.6	<0.001
CAP (dB/m)	247.0±49.9	251.0±39.7	0.31

CAP; *controlled attenuation parameter*, APRI; *AST/platelet ratio index*, FIB-4 score:*Fibrosis-4 index*

Table 4: Changes of the fibrosis stages pre-treatment and after SVR

Variables (n= 84)	Pre-treatment	After SVR	p-value
F0-F1	15 (17.8%)	19 (22.62%)	<0.001
F2	18 (21.4%)	23 (27.38%)	<0.001
F3	22 (26.3%)	18 (21.43%)	<0.001
F4	29 (34.5%)	24 (28.57%)	<0.001

Table 3 shows a statistically significant decrease (improvement) in the noninvasive parameters of liver fibrosis in our patients after achieving SVR, as regards the FIB4 index (p <0.01), APRI (p <0.01), liver stiffness (p <0.01) and a non-statistically significant increase in CAP (p = 0.31).**Table 4** shows significant fibrosis down staging of most of our patients after attaining SVR after therapy with DAA drugs (p <0.001).

Discussion

The advert for the new classes of DAAs has a dramatic improvement in the cure of more than 90% of the HCV patients with good welfare course [34-40].

In our study, the SVR by DAAs was 96.6%. In this study we found significant improvement in liver biochemical tests, AFP and platelet count after SVR. This was consistent with previous studies that declared significant improvement in liver functions after achieving SVR following DAAs therapy [6, 41-45]. Hsu et al. reported in his study a significant improvement in the liver biochemical tests, mainly transaminases and increase in median platelet count. The author explained this improvement due to reduction of the necro-inflammatory activity in chronic HCV patients who achieved SVR induced by DAAs [46]. Furthermore, Giannini et al. suggested that, suppression of necroinflammation improves production of thrombopoietin and is proposed to increased platelet count [47].

In this study, we found a significant improvement or decline in the noninvasive parameters of liver fibrosis; LSM, APRI, and FIB-4 indices. However, CAP didn't show a significant change in our patients before and after SVR24. Similar results were reported by Bachofner et al. and Elsharkawy et al. They found a significant decline in LS measurement and other noninvasive parameters of fibrosis including APRI, and FIB4 indices in patients achieved SVR12, as a result of improvement in necroinflammation (ALT and AST) and fibrosis (platelets) [29, 48]. Also, Hsu et al. reported a significant rapid decrease of FIB-4 and APRI indices following SVR 12 and, according to them, this decline is due to a rapid ALT and AST decrease due necroinflammation improvement and, to a less extent, to platelets increase due to improvement in fibrosis [46].to them, this decline is due to a rapid ALT and AST decrease due necroinflammation improvement and, to a less extent, to platelets increase due to improvement in fibrosis [46].

The current study showed a significant reduction in the LSM scores by using FibroScan after attaining SVR 24, which was supported by other studies that observed a reduction in LSM values by using elastography after virologic clearance [5, 6, 49, 50].

Our study patients showed a significant down staging of their fibrosis scores. Thus, these patients with advanced fibrosis (F3 and F4) constituted about 50% at SVR24 compared to 60.8% pre-treatment. This was supported by Shiha et al. who reported a reduction in the percentage of F3 and F4 patients following DAAs treatment [51].

Furthermore, Attia et al. reported that, liver stiffness improves in patients with cirrhosis, whereas non-cirrhotic patients show no true change in liver stiffness following DAAs-SVR. In their research, fibrosis improved in 87% of their patients with decompensated cirrhosis and clinically severe portal hypertension following HCV clearance with DAAS therapy [52]. Singh et al. reported that LSMs by TE decreased in their studied HCV subjects when followed for nearly one year after viral clearance. They showed that early reduction in LSMs was a result of improvement in neuroinflammatory activity [53]. Therefore, the use of LSMs during necroinflammatory resolution period is not essential for fibrosis staging and evaluation.

Our study had some limitations. First, it's a retrospective study at a single center with a relatively small sample size. Second, the lack of the biopsy and histopathologic correlations of the changes occurring during and after the study with the significant related cut-

off values. Third, the relatively short duration of the study. Fourth, patients with ascites were not included in this study due to the technical difficulty of elastographic evaluation of fibrosis and cirrhosis in these patients .

Conclusion

Achieving SVR in patients with chronic HCV infection treated with DAAs therapy was significantly associated with improvement in liver fibrosis and liver stiffness as evaluated by non-invasive measures including APRI, FIB-4, and LSM by using FibroScan.

List of abbreviations

APRI: AST to Platelet Ratio Index
CAP: controlled attenuation parameter
DAAs: direct-acting antiviral drugs
FIB-4: Fibrosis-4 score
HCV: hepatitis C virus
LS: liver stiffness
LSMs: liver stiffness measurements
SVR: sustained virologic response
TE: transient elastography

Declarations

Consent for publication: Participants provided a consent for the study findings to be published in Medical Journal of Viral Hepatitis.

Competing interests: The authors declare they have no competing interests.

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