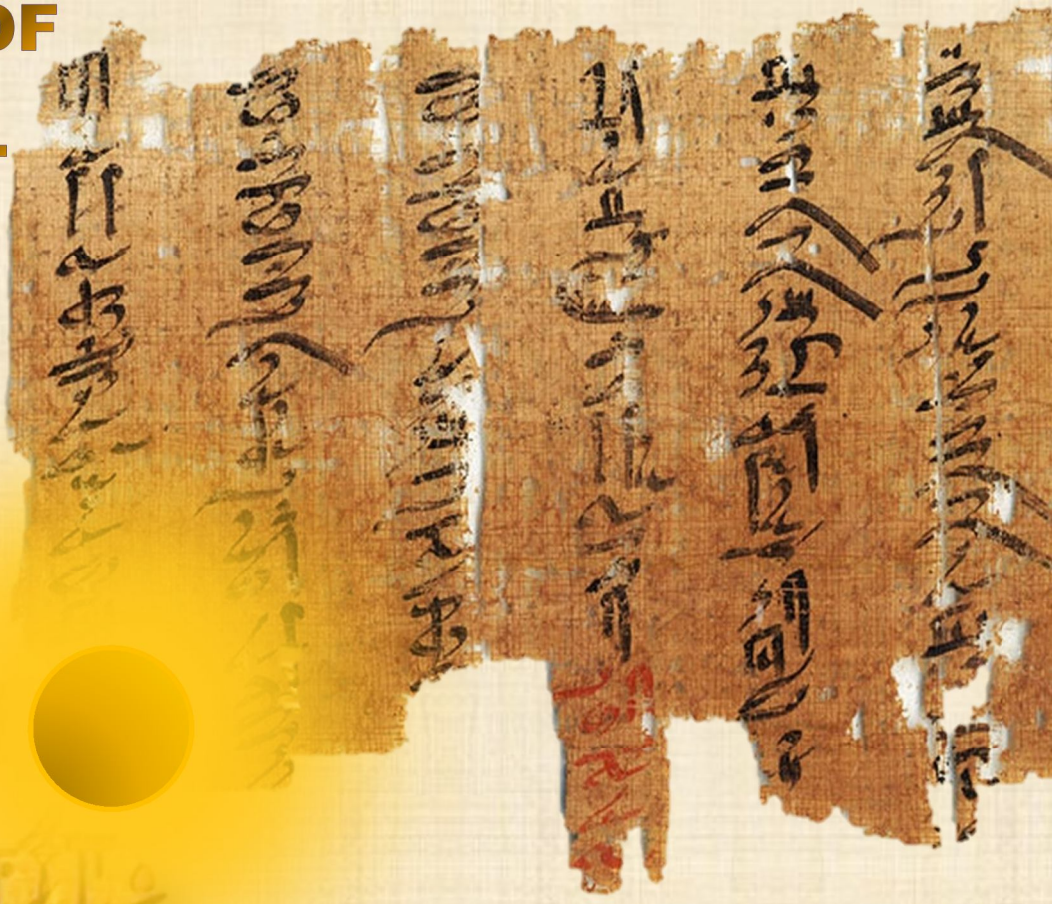
IJMA

International Journal of Medical Arts

VOLUME 2, ISSUE 4, AUTUMN 2020)



http://ijma.journals.ekb.eg/

Print ISSN: 2636 - 4174

Online ISSN: 2682 - 3780

International Journal of Medical Arts 2020; 2 [4]: 854-859.

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main subject [Medicine [Hepatology]] *

Original article

Effect of Successful Direct Acting Antivirals Therapy on Liver Stiffness in Patients with Chronic HCV Infection

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Received at: June 15, 2020; **Accepted at:** September 16, 2020

DOI: 10.21608/ijma.2020.23053.1138

ABSTRACT

Background: Achievement of sustained virological response [SVR] and improvement of hepatic fibrosis are the essential goals for therapy of chronic hepatitis C [CHC] with direct acting antivirals [DAAs] therapy. Early detection and management of hepatic fibrosis can significantly improve the prognosis of CHC in clinical practice.

Aim of the work: To assess the effect of successful DAAs therapy on liver stiffness in patients with CHC.

Methods: This study included 100 patients with chronic HCV-related liver disease. All were treated with Sofosbuvir-based regimen for 12 weeks on outpatient base. HCV treatment applied according to the protocol designed by the Egyptian National Committee for Control of Viral Hepatitis. Follow up continued for 12 weeks [after the end of treatment [EOT]] to estimate effect of successful DAAS therapy on liver stiffness using Shear Wave Elastography [SWE], aminotransferase-to platelet ratio index [APRI] and Fib-4 score before initiation of antiviral therapy, at end of treatment [EOT] and 12 weeks after EOT [SVR12].

Results: Platelets significantly increased, ALT and AST significantly decreased and mean values of APRI, Fib-4 score and Liver stiffness assessment were significantly reduced in all patients at SVR12. Hemoglobin levels significantly reduced in patients receiving ribavirin 12 weeks after EOT.

Conclusions: Elimination of HCV after successful DAAS treatment was associated with a significant improvement of the liver stiffness at both EOT and 12 weeks afterwards EOT as evidenced by SWE, Fib-4 score and APRI index.

Keywords: Direct acting antivirals; Elastography; Hepatitis C Virus; Liver fibrosis; sustained virological response.

Please cite this article as: Ezzelregal IA, Elraie FM, Shaqueer MM, Elmolla KA. Effect of Successful Direct Acting Antivirals Therapy on Liver Stiffness in Patients with Chronic HCV Infection. IJMA 2020; 854-859 2[4]: DOI: 10.21608/ijma.2020.23053.1138

* Main subject and any subcategories have been classified according to research topic.

INTRODUCTION

Chronic hepatitis C [CHC] represent a major public health problem, affecting about 200 million of worldwide population [1]. It is considered fundamental cause of hepatocellular carcinoma [HCC] and one of the indications of liver transplantation [2]. Liver fibrosis is a significant consequence of CHC, which may finally lead to cirrhosis and end-stage liver complications. Patients with absent or mild hepatic fibrosis have low risk of cirrhosis development[3].

The primary goal of HCV therapy is to eradicate the infection. Direct-Acting Antiviral [DAAs] therapies showed a promising future for HCV treatment with achievement of 99% successful sustained virological response [SVR]. After elimination of HCV, liver fibrosis may regress and the risk of HCV related complications were reduced[4].

Accurate and serial estimation of hepatic fibrosis is still desirable using noninvasive modalities. Several noninvasive markers like Fib-4 and aminotransferase-to platelet ratio [APRI] index have been demonstrated to be accurate in estimating hepatic fibrosis before antiviral therapy[6].

Moreover, they have been adjusted to follow-up patients with CHC and to assess the effect of antiviral treatment [7]. Liver Stiffness Measurement [LSM] applying Shear Wave Elastography [SWE] allowed non-invasive staging of liver fibrosis and cirrhosis with proven clinical accuracy [5].

Liver biopsy is still advised as the gold standard for assessment of liver fibrosis, even though it is painful, costly, and associated with restriction in diagnostic utility. Also, because the invasiveness of liver biopsy, repeated examinations are prevented[8], and longitudinal estimation of liver fibrosis is difficult. Thus, there is continuous search for non-invasive alternatives. Real-time SWE is a new ultrasound-based technique for non-invasive estimation of liver stiffness. This can easily and accurately assess the degree of liver fibrosis in clinical practice[9].

Also, the assessment of liver stiffness using imaging techniques such as SWE allow for non-invasive repeat estimation of liver fibrosis in patients with chronic liver disease, which allow for serial follow up of response to DAAs.

AIM OF THE WORK

The aim of the current study is to determine the effect of successful direct-acting antiviral therapy on liver stiffness in patients with CHC

PATIENTS AND METHODS

One hundred patients with HCV-related liver disease were included in the current study. They were selected from Hepatology, Gastroenterology and Infectious Disease Department, Al-Azhar University Hospital (New Damietta); between January and August 2019. All of them received antiviral therapy [Sofosbuvir- based therapy regimen] according to the protocol of HCV treatment lunched by the Egyptian National Committee for Control of Viral Hepatitis **[NCCVH, 2017]**.

Patients' characteristics were: age 18–75 years, HCV RNA positivity, treatment naïve or treatment experienced with any stage of hepatic fibrosis.

Patients were **excluded** if they had HBV co-infection, decompensated liver cirrhosis, un-controlled diabetes mellitus [HbA1c>9%], hepato-cellular carcinoma or extra-hepatic malignancy. Eligible patients were assigned to two groups according to treatment protocol; **Group I** received generic Sofosbuvir [400 mg] and Daclatasvir [60 mg]; treatment naïve with no evidence of cirrhosis], and **Group II** received the same regimen plus body weight-based Ribavirin [RBV; 1000 mg for <75 kg to 1200 mg for > 75 Kg] for 12 week on outpatient base.

Patients were subjected to full history taking, full clinical assessment, and laboratory investigations [Complete Blood Picture [CBP], Alanine Trans-aminase [ALT], Aspartate Transaminase [AST], and International Normalized Ratio [INR], serum albumin, total serum bilirubin, Alfa Fetoprotein [AFP], fasting blood sugar, serum creatinine, quantitative Polymerase Chain Reaction [PCR] for HCV RNA] and abdominal ultrasound before initiation of treatment, at EOT and 12 weeks after EOT.

Estimation of liver stiffness had been determined before initiation of treatment, at the EOT and at 12 weeks after EOT by calculating Aspartate-Platelet Ratio Index [APRI] and Fib-4 score and recording liver stiffness measurements [LSM]. APRI index was

calculated using Wai's formula: [AST/upper limit of normal]/platelet count [expressed as platelets x10^9/l] ×100[10].

Fib-4 score was calculated using Sterling's formula: Age [years] × AST [IU/l]/platelet count [x10^9/l] × √ALT [IU/l]] [9]. APRI cut-off > 1.0 predicts cirrhosis, while a cut-off > 0.7 predicts significant hepatic fibrosis[11]. FIB4 cut-off > 3.25 had a positive predictive value of 65% for advanced hepatic fibrosis, and cut-off < 1.45 had a negative predictive value of 90% for advanced hepatic fibrosis and cirrhosis. Liver stiffness [LS] evaluation were recorded for all patients with Shear Wave Elastography [SWE] study of liver using ultrasound machine [Aplio 500 system, Toshiba, Japan]. At least ten proper measurements were obtained, and median of LS described in kilopascals [kPa] were included. A success rate is determined as the ratio of valid readings to the total number of readings is more than 60%. Interquartile range reflect the fluctuation of LSM if less than 30%. Only examinations with success rate and Interquartile range were considered. Liver stiffness less than 7.1 kPa was considered as non-significant hepatic fibrosis [<F2], from at least 7.1 kPa to less than 9.5 kPa was considered as significant hepatic fibrosis [≥F2], at least 9.5 kPa was considered for advanced hepatic fibrosis [≥F3] and at least 12.5 kPa was considered for cirrhosis [F4][12,13]. The effect of successful DAAs therapy on liver stiffness was evaluated at end of treatment [EOT] and at 12 weeks after EOT [SVR_{12}].

Statistical Methods: IBM-SPSS statistical software package [version 22, New York, USA] was used for data analysis. Variables of quantitative type were described as means ± standard deviation of the means, while data of categorical type were presented as relative numbers and percentages. Differences between groups were analyzed either by using the Chi square test or student's [t] test and nonparametric [Mann Whitney test] for comparison between two groups. For observation of serial measurements [before and after] within each group the non-parametric Wilcoxon signed rank test or paired samples [t] test were used. P-values < 0.05 were considered as statistically significant.

RESULTS

Table [1] Showed baseline characteristic features of 100 Egyptian patients included in the study. They were 64 [51.2%] males and 61 [48.8%] females. All [100%] patients were treatment naïve and achieved sustained Virological response [SVR] with elimination of HCV-RNA at 12 weeks [SVR12] after EOT. Insignificant fibrosis was more evident in 34 [34%] patients. Fifty patients [50 %] were staged as F2-F3 and 16 patients [16%] had advanced fibrosis [F4].

Laboratory characteristics of the studied groups are showed in tables [2 and 3]. Platelets significantly increased, while ALT and AST levels significantly decreased in all patients 12 weeks after EOT. Hemoglobin levels significantly decreased in group II patients receiving ribavirin 12 weeks after EOT [Table.2]. No significant difference was noted in serum bilirubin, albumin, INR and AFP after treatment. Mean values of APRI, Fib-4 score and liver stiffness measurements were significantly reduced in all patients 12 weeks after EOT [Table 3].

Table [1]: Baseline characteristics of the studied patients

		Group I [Easy to treat] N=79	Group II [Difficult to treat] N=21	P value
Age [Years]		49.2±14.8	56.3±5.2	0.2
Gender	Male	42 [53.16%]	11 [53.38%]	0.53
	Female	37 [46.84%]	10 [47.62%]	
Treatment status	Naïve	100[100%]	100[100%]	a
	Experienced	0.0[0%]	0.0[0%]	
Treatment Response	Responder	79 [100%]	21 [100%]	a
	Non Responder	0.0[0%]	0.0 [0%]	
Fibrosis stage N [%]	< F2	34[43.00%]	0.0[0%]	<0.001*
	F2-F3	45 [57.00%]	5 [23.8%]	
	F4	0.0[0%]	16 [76.20%]	

a: No statistics could be computed as the variable is constant; * : significant difference

Table [2]: Laboratory features of patients in group I, before and after treatment

	Pre treatment	EOT	SVR12	p-value
Hemoglobin [g/L]	12.5±1.5	13.6±1.6	13.6±1.6	0.3
WBCs x10^3]/ cmm	6.5±1.9	6.5±0.8	6.5±0.8	0.2
Platelets x10^3]/ cmm	228±55	229.2±50.6	234.7±50.2	0.03*
ALT[U/L]	42±11.5	31.7±12.6	26.3±6.3	0.02*
AST[U/L[	46±12.7	30.7±11.8	26.3±6.3	0.03*
Albumin [g/dl]	4±0.4	4.1±0.3	4.1±0.3	0.2
Bilirubin [mg/dl]	0.9±0.3	0.9±0.2	0.9±0.2	0.96
INR	1.04±0.07	1.04±0.07	1.04±0.05	0.4
AFP [ng/dl[	8.7±3.2	8.7±3.2	8.7±3.2	0.7
HCV- RNA [log$_{10}$]	6.9±1.9	<15	<15	0.02*
FIB-4 score	1.8±0.6	1.4±0.5	1.1±0.4	0.03*
APRI index	0.8±0.3	0.6±0.2	0.5±0.1	0.02*
LSM	8.1±1.4	7.06±1.1	6.5±0.9	0.02*

WBCs: White Blood Cells; ALT: Alanine Transaminase; AST: Aspartate Transaminase; INR: International Normalized Ratio; AFP: Alfa Fetoprotein; HCV-RNA: Hepatitis C Virus-Ribosomal Nucleic Acid; APRI: Aspartate-platelet ratio index; LSM: Liver Stiffness Measurement; *: Statistically Significant

Table [3]. Laboratory features of patients in group II, before and after treatment

	Pre-treatment	EOT	SVR12	p-value
Hemoglobin [g/L]	11±1.8	10.8±1.6	10.7±1.6	0.03*
WBCs x103]/ cmm	5.4±1.8	5.1±0.7	5.1±0.7	0.2
Platelets x10^3]/ cmm	125.5±25	127±22.5	132±22	0.03*
ALT[U/L]	53.5±14.5	35±11.3	28±7	0.02*
AST[U/L]	57.9±14.5	33.4±13.3	27±6.8	0.03*
Albumin [g/dl]	3.5±0.3	3.6±0.2	3.6±0.2	0.2
Bilirubin [mg/dl]	1.2±0.4	1.1±0.1	1.2±0.1	0.96
INR	1.1±0.1	1.1±0.1	1.1±0.1	0.4
AFP [ng/dl]	9.1±3.3	9.2±3.3	9.2±3.3	0.7
HCV- RNA [log10]	6.8±1.9	<15	<15	0.02*
FIB-4 score	3.4±0.8	2.8±0.5	2.1±0.4	0.03*
APRI index	1.6±0.4	1.2±0.3	1±0.3	0.02*
LSM	11.6±1	10.1±0.9	9±0.8	0.02*

WBCs: White Blood Cells; ALT: Alanine Transaminase; AST: Aspartate Transaminase; INR: International Normalized Ratio; AFP: Alfa Fetoprotein; HCV-RNA: Hepatitis C Virus-Ribosomal Nucleic Acid; APRI: Aspartate-platelet ratio index; LSM: Liver Stiffness Measurement; *: Statistically Significant

DISCUSSION

Hepatitis C virus is considered one of the major causes of morbidity and death[14]. Chronic hepatitis C infection cause hepatic inflammation, which ultimately stimulates liver fibrosis[15]. Fibrosis becomes more harmful and progresses to liver cirrhosis[16]. Most HCV-associated hepatocellular carcinoma is seen with experience of liver fibrosis or cirrhosis[17]. Recent options of HCV treatment as DAAs can efficiently eradicate the virus, but regression of hepatic fibrosis in all patients is not the same. Liver fibrosis remains especially in patients with advanced hepatic fibrosis or cirrhosis[18]. So assessment of fibrosis after DAAs therapy is still necessary.

Although, liver biopsy remain the gold standard for staging of hepatic fibrosis, some drawbacks have been raised regarding its invasiveness, potential for adverse reactions and sample errors[19], rising interest of research for alternative, non-invasive diagnostic methods for the measurement of hepatic fibrosis[20]. Non-invasive serological markers have been validated to anticipate the presence of hepatic fibrosis with appropriate accuracy[21]. Shear Wave Elastography [SWE] is the greatest widely used imaging tool for quantitative judgment of hepatic stiffness by tracking shear waves propagating through the liver[22] and the aim of the current study is to estimate the effect of successful DAAs therapy on liver stiffness in patients with CHC by using SWE and other non-invasive guidance.

In this study, Platelets significantly improved, while ALT and AST levels, mean values of APRI, Fib-4 score and liver stiffness measurements were found to be significantly decreased in all patients 12 weeks after EOT [SVR12]. Our findings were in agreement with **Shousha et al.** and **Mansour et al.** who reported improvement in liver stiffness and fibrosis scores following Sofosbuvir based treatment regimen in chronic HCV patients[23,24].

Fib-4 and APRI index are affected by the cessation of activity of AST and ALT, and also by the improvement of platelets count identifying significant improvement of hepatic fibrosis and necro-inflammation following Sofosbuvir treatment[25].

Liver stiffness is affected not only by the stage of hepatic fibrosis but also by the degree of necro-inflammatory activity. In our study, platelets count, which corresponds to hepatic fibrosis, was not significantly change from baseline to EOT. So, reduction of ALT levels from baseline to EOT was strongly sided with the decline of liver stiffness measurements as shown by SWE. **Tada et al.**[26] considered that improvement of liver fibrosis was a gradual process beginning at EOT in patients who demonstrated HCV eradication as a result of DAA therapy.

Mansour et al.[24] raise a question about the most applicable time for starting estimation of liver stiffness after DAAs; either early at 12 weeks after EOT or later after treatment, and how much later. Also it was suggested that non-invasive imaging follow-up of CHC patients who achieved SVR should start weeks after EOT.

Conclusion: Elimination of HCV after successful DAAS treatment was enlisted with a significant improvement of the Liver Stiffness at both EOT and 12weeks after EOT as evidenced by SWE, FIB4 score and APRI index.

Financial and Non-financial Relationships and Activities of Interest

Authors declare no competing interest of any kind. The all funds of this research provided by authors themselves.

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International Journal of Medical Arts

https://ijma.journals.ekb.eg/
Print ISSN: 2636-4174
Online ISSN: 2682-3780