Al-Azhar Med. J.(Medicine). *Vol. 50(4), October, 2021, 2927-2936*
DOI: 10.21608/amj.2021.196431
https://amj.journals.ekb.eg/article_196431.html

ASSESSMENT OF LIVER FIBROSIS BEFORE AND AFTER DIRECT ACTING ANTIVIRAL THERAPY IN COMPENSATED HCV RELATED LIVER DISEASE

By

Ahmed Fathalla Khattab, Islam Ammar and Ahmed Mohamed Massoud

Department of liver, GIT and Infectious Diseases, Faculty of Medicine, Al-Azhar University

Corresponding Author: Ahmed Fathalla Khattab,

Phone: +201009619697, **E-mail:** ahmedkhattab315@gmail.com

ABSTRACT

Background: Hepatitis C virus (HCV) is a major health problem worldwide. Its long-term impact ranges from minimal damage to extensive fibrosis and cirrhosis, which is sometimes, accompanied by hepatocellular carcinoma (HCC).

Objective: To evaluate early changes of hepatic fibrosis-related parameters in patients with chronic HCV patients using sonography-based real time elastography (RTE) and serum parameters as APRI, FIB4 before and after sofosbuvir-based antiviral therapy.

Patients and methods: This study were conducted on 75 Egyptian patients with chronic hepatitis C who were collected from September 2019 and March 2020 at the National Hepatology and Tropical Medicine Research Institute Outpatient Clinics, Cairo, Egypt.

Results: The mean age of the studied patients was 49.6±11.34years, 33 (44%)of them were males while 42 (56%) were females. A history of diabetes was reported in 9 (12%) patients, while 6 (8%) of our patients were hypertensive. A total of 75 HCV-infected patients treated with sofosbuvir based therapy for 12 weeks were identified, 62 (82.7%) were treated with sofosbuvir (400 mg/day) and daclatasvir(60 mg/day) , 13(17.3%)were treated with sofosbuvir(400 mg/day)and daclatasvir(60 mg/day) with weight-based ribavirin.

Conclusion: Sofosbuvir-based treatment regimens for chronic hepatitis C resulted in significant reduction in liver stiffness measurements (LSM) by pSWE with significant changes in the distribution of patients receiving triple therapy among the fibrosis stages and significant improvement in fibrosis scores (FIB4 and APRI) 12 weeks post treatment.

Key words: Liver fibrosis, antiviral therapy and compensated HCV.

INTRODUCTION

Hepatitis C virus (HCV) is a major health problem worldwide. Its long-term impact ranges from minimal damage to extensive fibrosis and cirrhosis, which is sometimes, accompanied by hepatocellular carcinoma (HCC) *(EASL, 2014).*

The objective of chronic hepatitis C (CHC) treatment is to achieve a sustained virological response (SVR), defined as the absence of viral replication 12 or 24 weeks after treatment completion. A SVR which is stable over time, reduces morbidity and mortality, and is considered

in most cases to be equivalent to cured HCV infection *(van der Meer, 2012)*.

The objective of chronic hepatitis C (CHC) treatment is to achieve a sustained virological response (SVR), defined as the absence of viral replication 12 or 24 weeks after treatment completion. A SVR which is stable over time, reduces morbidity and mortality, and is considered in most cases to be routinely measured serum markers, used either individually or in combination, have been examined as alternatives for staging fibrosis among hepatitis C patients. Total billirubin, albumin, Platelet count *(Kelleher et al., 2015)*, the ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT), or a combination of AST and platelet count are reliable predictors of cirrhosis *(Wai et al., 2013)*.

Noninvasive approach to assessment of severity of hepatitis C include clinical symptoms and signs, routine biochemical and hematologic blood tests, serum markers of fibrosis and inflammation, combinations of clinical and blood test results, quantitative assays of hepatic function, and radiologic imaging studies. Although clinical and historical data have been shown to correlate with rate of fibrosis progression, their accuracy in predicting stage of fibrosis on liver biopsies is low *(Fontana and Lok, 2012)*.

Fibrosis-4 Score (FIB-4) and aspartate aminotransferase-platelet ratio index (APRI) scores have been validated for chronic hepatitis C (CHC) and show acceptable sensitivity and specificity, particularly in advanced fibrosis and cirrhosis *(Chou and Wasson, 2013)*. They have been demonstrated to be accurate in staging chronic liver diseases before antiviral treatment and prediction of hepatic fibrosis in HCV patients *(Yosry et al., 2016)*. Moreover, they have been used to longitudinally follow patients with chronic hepatitis and to assess the effect of antiviral treatment *(D'Ambrosio et al., 2013)*.

The aim of this work was to evaluate early changes of hepatic fibrosis-related parameters in patients with chronic HCV patients using liver stiffness measurement by Shear wave elastography (Siemens-Acuson S2000) and serum parameters as APRI, FIB4 before and after sofosbuvir-based antiviral therapy.

PATIENTS AND METHODS

This was a prospective cohort study that recruited 75 Egyptian patients with chronic hepatitis C who were collected and followed up during the period between September 2019 and March 2020. 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 National Hepatology and Tropical Medicine Research Institute outpatient clinics, one of the centers of National Committee for Control of Viral Hepatitis (NCCVH).

All of the patients were treated for 12 weeks and achieved SVR at week 12 post treatment. History taking and complete clinical examination were checked for all patients enrolled in the study. Liver biochemical profile included total and direct bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), serum albumin (ALB) and International normalized ratio (INR), complete blood count (CBC), HBsAg, HCV-Ab, HCV

PCR quantitative, serum creatinine, alpha-fetoprotein (AFP), fasting blood sugar (FBS), and HbA1c (if diabetic).

Liver stiffness measurement by FibroScan and Abdominal ultrasonography were applied for all participants to detect the echopattern of the liver (ultrasonographic features of cirrhosis), the degree of fibrosis, presence of signs of portal hypertension, maximum spleen bipolardiameter, and to exclude hepatocellular carcinoma.

FIB-4 index was calculated to all patients using the formula:

Age (years)×AST (U/L)/ [PLT(109/L)× ALT1/2 (U/L)]) *(Sterling et al., 2016).*

APRI score was calculated too using the equation:

[(AST/ ULN AST)x 100]/ Platelets (109/L)] *(Wai et al., 2013).*

Liver stiffness measurements (LSM) were recorded to all patients before treatment and 3 months after the end of treatment with the shear-wave elastography device (Siemens-Acuson S2000 VC25).

Statistical analysis: Continuous data were described as mean ± SD or median and Interquartile ranges (IQR), while categorical variables were presented as the count with corresponding percentages (n, %). For independent group comparisons, Mann Whitney U test for continuous non-normally distributed data, t-test for normally distributed data, and Chi-square test for ratios were utilized. For dependent (paired) group comparisons, Wilcoxon signed rank test for continuous non-normally distributed data, paired t-test for normally distributed data, and McNemar test for ratios were applied. A priori alpha of less than 0.05 was set for hypothesis testing. Normality of numerical data distribution was examined using the Shapiro-Wilk test. The bivariate correlation coefficients were estimated using Pearson correlation test for parametric data or Spearman test for non-parametric data. The statistical analyses were performed using SPSS for Windows (version 26.0, IBM Corp Armonk, NY, USA).

RESULTS

The mean age of the studied patients was 49.6±11.34 years, 33 (44%) of them were males while 42 (56%) were females. A history of diabetes was reported in 9 (12%) patients while 6 (8%) of our patients were hypertensive 3 (2.80%). A total of 75 HCV-infected patients treated with sofosbuvir based therapy for 12 weeks were identified, 62 (82.7%) were treated with sofosbuvir 400 mg/day and daclatasvir 60 mg/day and 13 (17.4%) were treated with sofosbuvir 400 mg/day and daclatasvir 60 mg/day with weight-based ribavirin (1000 mg (below 75 kg) to 1200 mg (above 75mg) **(Table 1)**.

Table (1): Baseline patient characteristics for all patients (n=75)

Patient characteristic	Mean±SD	range
Age (years)	49.6±11.34	22-72
Weight (Kg)	76.35±15.2	49-130
Height (Cm)	164.23±8.63	147-185
Body mass index (Kg/m^2)	28.4±5.85	19.14-49.95
Gender (n, %) **Males** **Females**	 33 (44%) 42 (56%)	
Smoking (n,%) **Smokers** **Non-smokers**	 16 (21.3%) 59 (78.7%)	
Hypertension (n, %)	6 (8%)	
Diabetes (n,%)	9 (12%)	
Treatment regimen (n, %) **400 mg Sofosbuvir+ 60 mg Daclatasvir** **400 mg Sofosbuvir+ 60 mg Daclatasvir ±RBV**	 62 (82.7%) 13 (17.3)	

All biochemical parameters associated with Liver function tests (serum total and direct bilirubin, serum albumin and INR), Renal function test(serum creatinine), Complete blood count parameters and Alpha fetoprotein (AFP) were normal except non-significant elevation in liver enzymes (ALT and AST) which were 45.44±20.39 mg/dl and 43.66±19.21mg/dl in diual therapy ,while were 56.46±42.12 mg/dl and 57.69±37.20 mg/dl in triple therapy **(Table 2)**.

Table (2): Comparing laboratory values between the treatment arms before treatment

Parameters \ Treatment	Sof/Dac (n=62)	Sof/Dac/RBV (n=13)	*p*†
ALT (IU/L)	45.44±20.39	56.46±42.12	0.63
AST (IU/L)	43.66±19.21	57.69±37.20	0.52
AFP (IU/L)	4.15±3.54	14.94±37.99	0.93
Creatinine (mg/dl)	0.81±0.18	0.93±0.17	**0.03**
Albumin (g/dl)	4.18±0.37	3.98±0.42	0.19
Glucose (mg/dl)	99.81±26.29	95.38±14.59	0.56
Total bilirubin (mg/dl)	0.69±0.20	1±0.58	**0.04**
Hemoglobin (g/L)	13.29±1.42	13.88±1.53	0.22
WBCs (x10^3)	7.7±2.3	6.78±1.56	0.25
Platelets (x10^3)	238.5±66.33	160.62±68.25	**0.002**
PC%	93.28±11.34	88.15±10.21	**0.03**
INR	1.06±0.13	1.08±0.09	0.2

There were significant improvements regarding liver enzymes (ALT and AST after treatment compared with baseline. There were significant differences in haemoglobin (Hb) level and platelets between baseline and after triple therapy (13.88±1.53 vs. 12.78±1.54) and (160.62±68.25 vs. 191.62±80.59) respectively **(Table 3)**.

Table (3): Comparing laboratory values before and after treatment in each study arm

Treatment / Parameters	Sof/Dac (n=62)			Sof/Dac/RBV (n=13)		
Status	Before treatment	After treatment	*P*	Before treatment	After treatment	*P†*
ALT (IU/L)	45.44±20.39	32.77±7.43	**<0.001**	56.46±42.12	32.69±10.14	**0.006**
AST (IU/L)	43.66±19.21	30.63±7.57	**<0.001**	57.69±37.2	31.08±9.45	**0.006**
AFP (IU/L)	4.15±3.54	3.49±2.05	0.28	14.94±37.99	4.01±2.29	0.89
Creatinine (mg/dl)	0.81±0.18	0.73±0.24	0.011	0.93±0.17	0.81±0.17	0.13
Albumin (g/dl)	3.93±0.28	3.96±0.23	0.81	3.75±0.43	4.02±0.35	0.08
Total bilirubin (mg/dl)	0.69±0.2	0.7±0.43	0.82	1±0.58	0.96±0.51	0.75
Hemoglobin (g/L)	13.29±1.42	13.73±2.07	0.07	13.88±1.53	12.78 ±1.54	**0.001**
WBCs (x10^3)	7.7±2.29	7.55±2.59	0.46	6.78±1.56	6.95±1.31	1
Platelets (x10^3)	238.5±66.3	270.48±71.63	0.02	160.62±68.25	191.62±80.59	**0.001**
PC%	93.28±11.34	94.1±11.32	0.88	88.15±10.2	82.77±15.62	0.29
INR	1.06±0.13	1.03±0.44	0.42	1.08±0.09	1.14±0.17	0.11

There were significant decreases in liver stiffness in both dual and triple therapy **(Table 4)**.

Table (4): Comparing non-invasive measures before and after treatment in each study arm

Treatment / Measures	Sof/Dac (n=62)			Sof/Dac/RBV (n=13)		
Status	Before treatment	After treatment	*P*	Before treatment	After treatment	*P†*
FIB4	1.69±1.27	1.03±0.44	**0.001**	1.98±1.91	1.23±0.55	**0.001**
APRI	0.54±0.33	0.33±0.14	**0.002**	1.13±0.89	0.54±0.32	**0.002**
Stiffness	8.11±4.98	7.2±3.4	**0.005**	16.59±18.69	11.66±10.12	**0.005**

DISCUSSION

This was a prospective cohort study aimed to evaluate early changes of hepatic fibrosis-related parameters in patients with chronic HCV patients using liver stiffness measurement, Shear wave elastography (Siemens-Acuson S2000) and serum parameters as APRI, FIB4 before and 3 months after end of sofosbuvir-based antiviral therapy. The current study showed that the mean age of the studied patients was 49.6±11.34 years with female predominance (56%).Seventy five of studied patients who all were Child–Pugh score A: 62 (82.7%) were treated with SOF/DCV for 12 weeks and 13 (17.4%) were treated with SOF/ DCV /RBV for 12 weeks according to the guidelines of the National Committee for Control of Viral Hepatitis (NCCVH) 2016. As regarding the treatment responses in the current study, the total sustained virological response (SVR) after 12 weeks was 100 % which come in accordance with *Welzel et al. (2016)* who showed use of SOF-DCV with or without RBV in patients with HCV and advanced liver disease .The

SVR12 rate was 100%.In the current study, regarding the liver enzymes indices; both ALT and AST levels significantly declined 3 months after end of treatment among all studied patients came in accordance with *Ahmed et al. (2018)* who reported significant reduction in AST and ALT level for both 3 months after end of treatment. Similarly *Elsharkawy et al. (2017)* discussed the impact of sofosbuvir based treatment regimen on the biochemical profile of chronic hepatitis C patients discussed and concluded that DAAs improve liver necro-inflammatory markers in cirrhotic and non-cirrhotic. The current study showed that hemoglobin concentration was significantly declined 3 months after end of triple therapy due to RBV administration. This finding was previously reported by *Wu et al. (2016)* who suggested that RBV is a triggering factor of hemolytic anemia, and RBV combination with SOF revealed a decrease in hemoglobin concentration.

The current study showed significant improvement in platelet count 3 months after end of triple therapy that *Elsharkawy et al. (2017)* reported in their cirrhotic patients. The current study showed significant declination in FIB4 score 3 months after end of both diual and triple treatment. Also, the study showed significant declination in APRI score 3 months after end of both diual and triple treatment. These results came in accordance with *Shousha et al. (2017)* who showed significant improvement in FIB4 and APRI 3 months after end of Sofosbuvir based treatment. This could be explained by the significant improvement in parameters of liver fibrosis as ALT and AST levels after completing treatment regimens, which were reflected on FIB-4 and APRI. The current study showed significant reduction in liver stiffness measurements by pSWE 3 months after end of antiviral therapy which came in accordance with *Shousha et al. (2017)* who showed rapid significant reduction in liver stiffness measurements as measured by transient elastography 3 months after end of sofosbuvir-based treatment.

CONCLUSION

Sofosbuvir-based treatment regimens for chronic hepatitis C resulted in significant reduction in liver stiffness measurements (LSM) by pSWE and significant improvement in fibrosis scores (FIB4 and APRI) 12 weeks post treatment.

REFERENCES

1. **Ahmed OA, Safwat E, Khalifa MO and El shafia A. (2018):** Sofosbuvir Plus Daclatasvir in Treatment of Chronic Hepatitis C Genotype 4 Infection in a Cohort of Egyptian Patients: An Experiment the Size of Egyptian Village. Int J Hepatol., 9(6): 162-74.
2. **Chou R and Wasson N. (2013):** Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. Ann Intern Med., 159: 372.
3. **D'Ambrosio R, Aghemo A, Fraquelli M and Rumi MG. (2013):** The diagnostic accuracy of Fibroscan for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. J. Hepatol., 59: 251–6.
4. **Elsharkawy A, Alem SA, Fouad R and EL Raziky M. (2017):** Changes in liver stiffness measurements and fibrosis scores following sofosbuvir based treatment regimens without interferon. J Gastroenterol Hepatol., 32(9): 1624-1630.
5. **European Association for Study of the Liver (EASL). (2014):** Clinical Practice

Guidelines: management of hepatitis C virus infection. J Hepatol., 60(2): 392-420.

6. **Fontana RJ and Lok AF. (2012):** Noninvasive monitoring of patients with chronic hepatitis C. Hepatology., 36: S57-S64.
7. **Kelleher T, Mehta S, Bhaskar R and Sulkowski M. (2015):** Prediction of hepatic fibrosis in HIV/HCV co-infected patients using serum fibrosis markers: The SHASTA index. J Hepatol., 43(1): 78-84.
8. **Omran D, Alboraie M and Zayed AM. (2016):** Towards hepatitis C virus elimination: Egyptian experience, achievements and limitations, World Health Organization (WHO), Hepatitis C Fact sheet.
9. **Shousha HI, Mehassab MK, Mehrez MI and Afifi SA. (2017):** Non-Invasive Fibrosis Scores and Liver Stiffness Changes in Chronic Hepatitis C after Sofosbuvir-based Treatment. Int J Hepatol Gastroenterol.,3(4): 085-090.
10. **Sterling RK, Lissen E, Clumeck N and Sola R. (2016):** Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co-infection. Hepatology, 43: 1317-1325.
11. **van der Meer AJ. (2012):** Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA, 308(24): 2584-93.
12. **Wai CT, Greenson JK, Fontana RJ and Kalbfleisch JD. (2013):** A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology.,38: 518-26.
13. **Welzel TM, Petersen J, Herzer K and Ferenci P. (2016):** Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut., 65: 1861-1870.
14. **Wu LS, Jimmerson LC, Mac-Brayne CE and Kiser JJ. (2016):** Modeling ribavirin-induced anemia in patients with chronic hepatitis C virus.CPT Pharmacometrics Syst Pharmacol., 5(2): 65–73.
15. **Yosry A, Fouad R, Alem SA, Elsharkawy and El sayed M. (2016):** Fibroscan, APRI. FIB4, and GUCI: Role in prediction of fibrosis and response to therapy in Egyption patients with HCV infection. Arab J Gastroenterol, 17(2):78-83.

تقييم درجة التليف الكبدى قبل وبعد العلاج بمضادات الفيروسات المباشرة فى مرضى التليف الكبدى المتكافئ نتيجة فيروس سى

أحمد فتح الله خطاب خطاب، إسلام عمار، أحمد محمد مسعود

قسم امراض الكبد والجهاز الهضمى والامراض المعدية، كلية الطب، جامعة الأزهر

E-mail: ahmedkhattab315@gmail.com

خلفيـــة البحـــث: نهـدف مـن عـلاج التهـاب الكبـد المـزمن (سـى) الـى تحقيـق إسـتجابة فيروسـية متواصـلة والتـي تعـرف بعـدم وجـود تكـاثر للفيـروس فـي الاسـبوع 12 أو 24 بعـد اسـتكمال العـلاج و الاسـتجابة الفيروسـية المتواصـلة مسـتقرة مـع مـرور الوقـت، وتقلـل مـن معـدلات الاعـتلال والوفيـات، وهـى تعـادل فـي معظـم الحـالات الشـفاء مـن الالتهـاب الكبـد الفيروسـى (سـى). وتليـف الكبـد هـو العامـل الرئيسـى الـذى يحـدد فيـروس الالتهـاب الكبـدى الوبـائى سـى للأمـراض والوفيـات المرتبطـة. بالإضـافة إلـى ذلـك، فـإن مرحلـة التليـف هـي نـذير وتـوفر معلومـات عـن إحتمـال تطـور المرض والاستجابة للعلاج.

الهـدف مـن البحـث: تقيـيم التغيـرات المبكـرة مـن علامـات التليـف فـي المرضـى الـذين يعـانون مـن مرضـى التهـاب الكبـد الوبـائي المـزمن (سـى) باسـتخدام قيـاس صـلابة الكبـد باسـتخدام موجـه القـص الاسـتوجرافى فـى المرضـى المصـابين بالالتهـاب الكبـدى الفيروسـى سـى أثنـاء عـلاج مرضـى الالتهـاب الكبـدى الفيروسـى (سـى) بمضـاد الفيروسـات سوفوسـبوفيروذلك باسـتخدام قيـاس صـلابة الكبـد ابـرى، فيـب 4 وغيرها من العلامات غير الغازية التى تعبر عن درجه التليف.

المرضـــي وطـــرق البحـــث: هـذه دراسـة جماعيـة مسـتقبلية اجريـت علـي 75 مريضًـا مصـابًا بالتهـاب الكبـد الوبـائي المـزمن الـذين تـم جمعهـم ومتـابعتهم فـي الفتـرة مـا بـين يوليـو 2018 وسـبتمبر 2019 وتـم تقيـيم جميـع المرضـى للعـلاج المضـاد للفيروسـات وفقًـا لإرشـادات اللجنـة القوميـة لمكافحـة الفيروسـات الكبديـة فـى عيـادة عـلاج التهـاب الكبـد الفيروسـي فـي معهـد الكبـد القـومى بالقـاهره، وتلقـى جميـع المرضـى المرشـحين سوفوسـبوفير(400 مـج مـرة واحـدة يوميًـا) و داكلاتـازفير (60 مـج مـرة واحـدة

يوميًا) مع أو بدون ريبافيرين على أساس الوزن (1000 مج {أقل من 75 كجم} إلى 1200 مج {أعلاه 75 مج}.

وإذا إنخفض مستوى الهيموجلوبين أقل من 10 جم يتم تعديل جرعة الريبافيرين بتخفيضها إلى 200 مج وتوقف إذا كان مستوى الهيموجلوبين ينخفض اقل من 8.5 جم لمدة 12 أسبوعا ومتابعتها بانتظام في 4، 8، 12 أسبوعا.

نتائج البحث: كان عدد المرضى الذين بداوا واستكملوا متابعة العلاج 75 مريضا منهم 62 مريض تلقوا العلاج بسوفوسبوفير (400 مج مرة واحدة يوميًا) وداكلاتازفير (60مج مرة واحدة يوميًا), و13 مريض تلقوا العلاج ب سوفوسبوفير (400 مج مرة واحدة يوميًا) وداكلاتازفير (60 مج مرة واحدة يومياً) مع ريبافيرين على أساس الوزن (1000 مج {أقل من 75 كجم} إلى 1200 مج {أعلاه 75 مج}.

وكان متوسط عمر المرضي بين49.6±11.34 سنة, وكان نحو 56% منهم من الإناث بينما 44% من الذكور, ومنهم 12%مرضي يعانون من مرض السكري وكما كان8% مرضى يعانون من ارتفاع ضغط الدم.

الاستنتاج: نظام العلاج القائم على السوفوسبوفير لعلاج مرضي فيروس الاتهاب الكبدي سي يؤدي إلى انخفاض كبير في قياسات تصلب الكبد و تحسن كبير فى علامات المصل للتليف فيب 4 وابرى بعد إنتهاء العلاج باثنى عشر اسبوعا.

الكلمات الدالة: التليف الكبدى و العلاج الفيروسى و فيروس سى.