Effect of Direct Acting antivirals (DAAs) on Improvement of Liver Fibrosis Assessed by Transient Elastography and Associated Risk Factors for Accelerating Liver Fibrosis

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Abstract

Background: Egypt started a national treatment program intending to provide cure for Egyptian HCV-infected patients. Yet, with the development of highly-effective direct acting antivirals (DAAs) for HCV, elimination of viral hepatitis has become a real possibility. **This study aimed** to evaluate the impact of DAAs on achievement of improvement in liver fibrosis, and to evaluate risk factors associated with progression of liver fibrosis in patients achieved sustained virological response (SVR**). Method:** the study included 300 patients diagnosed with chronic HCV infection started their treatment protocol form 2016 who were divided into two groups; Group I (150 patients) included patients who received Sofosbuvir + Simeprevir ± Ribavirin as dual or triple therapy (for 12 weeks) for HCV treatment, and Group II (150 patients) included patients who received Sofosbuvir + Daclatasvir ± Ribavirin as dual or triple therapy (for 12 weeks) for HCV treatment. All cases were subjected to complete history taking, thorough physical examination, routine laboratory investigations, pelviabdominal US together with transient elastography were ordered for all cases. **Results**: both HCV treatment regimens showed improvement in liver fibrosis, fibro scan parameters showed a significant decrease in both groups compared to the baseline as pretreatment examination revealed mean values of 9.81 and 9.75 in both groups respectively. After treatment, both groups had mean values of 8.11 and 8.05. Both groups showed a significant change compared to its pre-treatment value ($p < 0.001$). There was a significant negative correlation between fibro scan parameter decrease with age, BMI, and HbA1C levels. There was no difference in degree of improvement of liver fibrosis between both regimens. **Conclusion:** fibrosis regressed significantly after DAAs

therapy regardless the treatment regimen. Also, there was a significant negative correlation between fibro scan parameter decrease with age, BMI, and HbA1C levels.

Keywords: DAAs; liver; fibrosis; elastography

Introduction

Hepatitis C Virus (HCV) infection is a major global health challenge; it is estimated that more than 80 million people are chronically infected worldwide, with 3-4 million new infections and 350,000 deaths occurring annually because of HCV-related complications. Hepatitis C viral infection is endemic in Egypt with the highest prevalence rate in the world, estimated nationally with around 14.7%. (1).

HCV causes progressive liver damage that only becomes apparent over a decade or more, when it culminates in Hepatocellular carcinoma or liver failure. By 2015 hepatitis C accounted for 40,000 deaths per year in Egypt (2).

There has been a spectrum of treatments to target the public health problem represented by the hepatitis C problem in Egypt: from the use of pegylated interferon to the recent use of direct acting antiviral drugs which have shown about 90% efficacy. However, cost is a key barrier to access these new medicines. This is coupled with a growing population, limited resources, and a lack of infection control practices which means Egypt still faces significant disease control issues today (3).

Transient elastography (FibroScan®) is a non-invasive device that assesses the stiffness of the liver. Transient elastography (FibroScan) is an attractive method for obtaining repeated measurements because it eliminates the pain, morbidity, and mortality that can accompany liver biopsy. Liver stiffness is evaluated by measuring the velocity of a vibration wave (which called a ‘shear wave’) generated on the skin. Shear wave velocity is determined by measuring the time that the vibration wave takes to travel to a particular depth inside the liver (4).

FibroScan® is principally used to estimate the degree of liver scarring present (i.e. stage of liver disease). This is very useful in the assessment of patients with chronic liver disease, including chronic hepatitis C, chronic hepatitis B, chronic alcohol abuse

and fatty liver. The concept is that as more fibrosis and scarring occur, the higher the liver stiffness reading will be. This reading may be used to: Estimate the existing degree of liver damage, monitor disease progression or regression via serial measurements and guide prognosis and further management, including treatment. (5)

It is still questionable whether new DAAs can improve liver stiffness or not and what are risk factors of preventing such improvement.

This study aimed to evaluate the impact of DAAs on achievement of improvement in liver fibrosis, and evaluate risk factors associated with progression of liver fibrosis in patients achieved sustained virological response (SVR).

Patients and methods

This prospective study was conducted on 300 patients who was previously successfully treated from chronic HCV infection and attending clinics of Hepatology and Gastroenterology at Police Hospitals (El-Agouza and New Cairo Police Hospitals) for HCV treatment in the period between August 2016 and October 2016 and achieved S.V.R.

All the participating cases in the study had written informed consent. The study was approved by the Ethical committee of Benha faculty of medicine.

Patients were divided into two groups according to their previous regimen of HCV treatment:

Group I (n= 150): Patients who received Sofosbuvir + Simeprevir ± Ribavirin as dual or triple therapy (for 12 weeks) for HCV treatment.

Group II (n= 150): Patients who received Sofosbuvir + Daclatasvir ± Ribavirin as dual or triple therapy (for 12 weeks) for HCV treatment.

Inclusion criteria:

- Patients with 18 years old or more.
- Patients with F2-F3 by fibroscan.
- Previously successfully treated from HCV infection in period from August 2016 to October 2016 and negative HCV PCR 2 years post treatment.

Exclusion criteria:

- F0 to F1 and F4 patients by fibroscan.
- Patients with decompensated cirrhosis.
- Co- infection with HBV or HIV.
- Auto-immune hepatitis.

- Cholestatic liver diseases as PSC and PBC.
- HCC.
- Patients with significant alcohol consumption.

All patients were submitted to full history taking, complete clinical examination, and laboratory investigations as; Complete blood count (CBC): hemoglobin (Hb), white blood cells (WBCs) and Platelets count, Full liver profile: (Pretreatment – End of treatment), Renal function tests, HBA1C, Viral markers: HBs Ag (Hepatitis B virus surface antigen) and HIV Ab), Quantitative PCR for HCV RNA at the end of treatment, 12 weeks post treatment and 2 years post treatment, and Serum α feto protein (AFP) (ng/dl).

Abdominal ultrasonography pretreatment by Phillips ClearVue 850® using 3.5 MHz probe for evaluation of **liver:** size, texture, border, reflectivity, homogenesity, periportal thickening, hepatic veins and pattern, suspected focal lesions, **portal vein:** diameter, patency, direction of flow, respiratory variation and velocity by color Doppler assessment, **spleen:** size, splenic vein diameter, collaterals, presence of ascites and internal echoes, lymph nodes and extrahepatic spread and portal hypertension and superior mesenteric vein patency.

Transient Elastography (Fibroscan) on liver pre-treatment, 2 years post treatment, FibroScan (FibroScan® 502 Touch, France) is performed on the right lobe of the liver by well qualified trained physician at El-Agouza Police Hospital. A total of 10 measurements, expressed in kPa, are obtained at each assessment and the median is determined. LS values are used to estimate the METAVIR fibrosis stage as follows: F0-F1: <7 kPa; F2: 7.0 to 9.4 kPa; F3: 9.4 to 12.4 kPa; F4: ≥ 12.5 kPa. Advanced fibrosis is defined as a median LSM level of ≥ 9.5 kPa in this study

Statistical Analysis

The data were coded, entered and processed on computer using *SPSS* (version 18). The results were represented in tabular and diagrammatic forms then interpreted. Mean, standard deviation, range, frequency, and percentage were use as descriptive statistics. The following test was done: Chi-Square test X^2 was used to test the association variables for categorical data. Student's T-test was used to assess the statistical significance of the difference between two population means in a study involving independent samples. ANOVA (F test) For normally quantitative variables, to compare between more than two groups, and Post Hoc test (LSD) for pairwise comparisons. R Pearson's Product correlation

coefficient: it evaluates the linear association between 2 quantitative variables (one is the independent vararіable X, and the other is the dependent var., Y). P value was considered significant as the following: * P > 0.05: Nonsignificant, * P ≤ 0.05: Significant

Results

This study was conducted on 300 patients who was previously successfully treated from chronic HCV infection in the period between August 2016 and October 2016 and achieved S.V.R, and they were divided into two groups according to their treatment regimen. **Group I (n= 150)**: Patients who received Sofosbuvir + Simeprevir ± Ribavirin as dual or triple therapy (for 12 weeks) for HCV treatment., **Group II (n= 150):** Patients who received Sofosbuvir + Daclatasvir ± Ribavirin as dual or triple therapy (for 12 weeks) for HCV treatment.,

The mean age of the included cases was 47.87 and 48.26 years for groups I and II respectively. Males represented 52.7 and 57.3% of cases in the both groups respectively. The mean values of BMI were 30.81 and 30.7 kg/m2 in both groups, respectively. Smokers represented 72 and 70.7% of cases in both groups, respectively. Previous ribavirin intake was reported by 12.7 and 9.3% of cases in both groups, respectively. Neither of the previous parameters was significantly different between the two studied groups (p > 0.05). Table 1

No difference was detected between the two study groups as regard the three main parameters of CBC (Hb, WBCs, and Plts). ALT values did not differ between the two groups neither before nor after treatment. Although AST did not significantly differ between the two groups before treatment, it showed significant decrease after treatment in group II. The remaining liver function tests including albumin, bilirubin, and INR were not significantly different between the two study groups. Both urea and creatinine did not show significant differences between the two groups. Serum alpha fetoprotein had mean values of 4.63 and 4.7 ng/ml in both groups respectively. The mean values of HbA1C were 6.23 and 7.08 in both groups respectively. It had significantly lower values in group I compared to group II (Table 2).

As regard fibro scan findings, pretreatment examination revealed mean values of 9.81 and 9.75 in both groups respectively. After treatment, both groups had mean values of 8.11 and 8.05. Both groups showed a significant change compared to its pre-treatment value. There was no significant

difference between the two groups regarding stage of fibrosis neither before nor 2 years post treatment. Nevertheless, each group showed a significant improvement in stage of fibrosis compared to the pre-treatment stage of fibrosis ($p < 0.001$). Table 3&4

There was no significant relation between fibro scan changes in either groups with gender, smoking, and ribavirin. Table 5

In both groups, there was a significant negative correlation between fibro scan parameter decrease with age, BMI, and HbA1C levels. Table 6

Table (1): Comparison between the two studied groups according to age, gender, BMI, smoking and ribavirin use

	Group I Patients received Sofosbuvir + Simeprevir ± Ribavirin **(n = 150)**		**Group II** Patients received Sofosbuvir + Daclatasvir ± Ribavirin **(n = 150)**		**Test of Sig.**	**p**
	No.	**%**	**No.**	**%**		
Gender						
Male	79	52.7	86	57.3	χ^2= 0.660	0.417
Female	71	47.3	64	42.7		
Age (years)						
Min. – Max.	21.0 –72.0		22.0 –72.0		t= 0.306	0.760
Mean ± SD.	47.87 ±12.35		48.26 ±9.80			
Median (IQR)	47.50 (40.0 –55.0)		49.0 (42.0 –53.0)			
BMI (m^2/kg)						
Min. – Max.	22.0 –41.0		22.0 –38.0		t= 0.552	0.581
Mean ± SD.	30.81 ±4.09		30.57 ±3.64			
Median (IQR)	30.0 (28.0 –34.0)		30.0 (28.0 –34.0)			
Smoker						
Yes	108	72.0	106	70.7	0.065	0.798
No	42	28.0	44	29.3		
Ribavirin						
Yes	19	12.7	14	9.3	0.851	0.356
No	131	87.3	136	90.7		

χ^2: Chi square test t: Student t-test p: p value for comparing between the studied groups

Table (2): Comparison between the two studied groups according to HbA1c pretreatment

HbA1c	**Group I** Patients received Sofo + Simep ± Ribavirin **(n = 150)**	**Group II** Patients received Sofo + Daclata ± Ribavirin **(n = 150)**	t	p
Min. – Max.	4.50 – 14.0	4.10 – 14.40		
Mean ± SD.	6.23 ± 2.01	7.08 ± 2.12	3.561*	<0.001*
Median (IQR)	5.70(4.90 – 7.0)	6.30(5.50 – 8.0)		

t: Student t-test
p: p value for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$

Table (3): Comparison between the two studied groups according to fibro scan score pretreatment and 2 years post treatment

Fibro scan	**Group I** Patients received Sofo + Simep ± Ribavirin **(n = 150)**	**Group II** Patients received Sofo + Dacla ± Ribavirin **(n = 150)**	Test of Sig.	p
Pretreatment				
Min. – Max.	7.20 –12.40	7.20 –12.40		
Mean ± SD.	9.81 ±1.54	9.75 ±1.61	t= 0.370	0.712
Median (IQR)	10.0 (8.50 –11.0)	9.60 (8.30 –11.0)		
2 years post treatment				
Min. – Max.	5.60 –11.40	5.60 –11.80		
Mean ± SD.	8.11 ±1.45	8.05 ±1.44	t= 0.316	0.752
Median (IQR)	8.15 (6.80 –9.30)	8.0 (6.90 –9.20)		
Change in score pre and post treatment	↓1.71 ±0.76	↓1.69 ±0.77	U=11224.0	0.972

t: Student t-test U: Mann Whitney test
p: p value for comparing between the studied groups

Table (4): Comparison between the two studied groups according to stage of fibrosis pretreatment and 2 years post treatment

Fibro scan	**Group I** Patients received Sofo + Simep ± Ribavirin **(n = 150)**		**Group II** Patients received Sofos + Dacla ± Ribavirin **(n = 150)**		χ^2	p
	No.	%	No.	%		
Pretreatment						
F0 – F1 (≤7)	0	0.0	0	0.0		
F2 (>7 – 9.4)	67	44.7	69	46.0	0.054	0.817
F3 (9.5 – 12.4)	83	55.3	81	54.0		
Post treatment						
F0 – F1 (≤7)	45	30.0	42	28.0		
F2 (>7 – 9.4)	73	48.7	80	53.3	0.690	0.708
F3 (9.5 – 12.4)	32	21.3	28	18.7		
^{MH}p	<0.001*		<0.001*			

χ^2: Chi square test
p: p value for comparing between the studied groups
^{MH}p: p value for Marginal Homogeneity Test comparing between pre and post in each group
*: Statistically significant at $p \leq 0.05$

Table (5): Relation between change in fibroscan score and different parameters in both studied groups

	N	change in fibroscan score			U	p
		Min. – Max.	Mean ± SD.	Median		
Group I Patients who received Sofo + Simep ± Ribavirin **(n = 150)**						
Gender						
Male	79	–0.80 – 3.0	1.63 ± 0.81	1.80	2698.50	0.689
Female	71	–0.50 – 3.80	1.80 ± 0.70	1.80		
Smoker						
No	42	–0.80 – 3.80	1.73 ± 0.78	1.80	2211.50	0.813
Yes	108	–0.80 – 3.80	1.73 ± 0.78	1.80		
Ribavirin						
No	131	-0.80 – 3.80	1.77 ± 0.70	1.90	903.0	0.053
Yes	19	–0.70 – 2.50	1.27 ± 1.0	1.60		
Group II Patients who received Sofos + Dacla ± Ribavirin **(n = 150)**						
Gender						
Male	86	–0.90 – 3.40	1.64 ± 0.84	1.80	2576.50	0.504
Female	64	0.20 – 3.10	1.77 ± 0.65	1.80		
Smoker						
No	44	–0.80 – 3.40	1.69 ± 0.86	1.70	2330.50	0.995
Yes	106	–0.90 – 3.10	1.70 ± 0.73	1.80		
Ribavirin						
No	136	–0.90 – 3.40	1.71 ± 0.76	1.80	794.50	0.308
Yes	14	–0.80 – 2.40	1.52 ± 0.81	1.75		

U: Mann Whitney test p: p value for association between different categories

Table (6): Correlation between change in fibroscan with different parameters in each group

	Decrease in fibroscan			
	Group I Patients who received Sofosbuvir + Simeprevir ± Ribavirin **(n = 150)**		**Group II** Patients who received Sofosbuvir + Daclatasvir ± Ribavirin **(n = 150)**	
	r_s	p	r_s	p
Age (years)	-0.366*	<0.001*	-0.472	<0.001*
BMI (m^2/kg)	-0.274	0.001*	-0.188	0.022*
Hgb	0.011	0.889	0.071	0.391
TLC (*1000)	-0.099	0.230	-0.004	0.960
Plt (*1000)	-0.044	0.596	-0.044	0.594
ALT	0.067	0.414	0.006	0.938
AST	-0.038	0.643	0.015	0.856
Serum Albumin (g/dl)	-0.092	0.263	0.053	0.521
PCR for HCV RNA	-0.056	0.498	0.127	0.120
HBA1c	-0.309	<0.001*	-0.506	<0.001*

rs: Spearman coefficient *: Statistically significant at $p \leq 0.05$

Discussion

In this study, there was no significant difference in the mean fibroscan value between the two groups pre and 2 years post treatment, however there was a statistically significant decrease in fibroscan score in each group 2 years post treatment as compared with the pretreatment value as pretreatment examination revealed mean values of 9.81 and 9.75 in both groups respectively. After treatment, both groups had mean values of 8.11 and 8.05. For each group, there was significant decrease of the post treatment values compared to its pre-treatment value ($p<0.001$). Also, in this study, according to the fibroscan grades, all the cases before treatment in the two groups were at grade F2 and F3 with no cases at grade F0-F1. After treatment, there was a significant improvement in the degree of fibrosis in each group. In group I 45 cases their fibrosis stage changed to F0-F1, in group II 42 cases their fibrosis stage changed to F0-F1.

These improvements are largely attributable to changes in the biochemical parameters of serum bilirubin and albumin. The results for SVR observed in these studies are indeed impressive, given that the majority of these patients had several characteristics that would predict a poor response.

This came in agreement with the study which assessed the impact of DAAs on fibrosis regression in chronic HCV patients with either compensated (F2) or decompensated liver disease (≥F3) (7) . The results demonstrated significant serial improvements of FIB-4 index and APRI score by FibroScan along the follow-up periods (EOT, 6-months and 12-months post-treatment) in chronic HCV patients with SVR12 after DAAs treatments. These non-invasive fibrosis markers improved significantly regardless of the patient's baseline fibrosis grade.

It was reported that in both groups with or without fibrosis/ histological improvement, the APRI showed a highly significant decrease after DAAs treatment ($p< 0.001$). However, in the fibrosis improvement group, the rate of FIB-4 reduction was significantly higher than that of no fibrosis group ($P = 0.017$) (8).

Other researchers also reported improvement of fibrosis scores such as FIB-4 and APRI in LT patients receiving sofosbuvir-based therapy (9).

In 2018, it was shown that FIB-4 index was significantly associated with improvement in liver stiffness measurements (using fibroscan measurement) after successful DAA therapy at univariate analysis, whereas viral load was the only significant predictor of improvement in liver stiffness measurements at SVR24 on multivariate regression analysis (10).

This comes in agreement with another prospective study which evaluated dynamics of liver and spleen stiffness in HCV patients using fibroscan with advanced liver disease and SVR after DAA treatment also found that improvement in liver stiffness may be rather due to reduced necroinflammation and may be due to a less extent to fibrosis regression (11).

This is supported by other studies also demonstrated a significant reduction in APRI values, and they suggested that early reduction in the APRI value mostly reflected reduction in necroinflammation rather than in fibrosis regression (12).

However, the exact mechanism still needs further studies for clarifying the mechanism responsible for reduction of these different parameters.

In the current study, only age, BMI and HBA1c showed statistically significant negative correlation with the improvement in fibroscan measurement in both study groups.

In this study, there was statistically significant negative correlation between improvement of the fibroscan with age, BMI and HBA1C.

Similar results were reported that older age was associated with an increased risk of poorly change in liver stiffness measurement. It was also reported that BMI was associated with nearly threefold odds of poorly reliable results. In a sub analysis including 434 patients with body mass index data, obesity influenced the rate of poorly reliable results (13).

Our results come in agreement with others who reported highly significant improvement of liver fibrosis after weight loss ($p<0.01$) (14).

This was also agreed with the previously reported results where older age was associated with an increased risk of poor response in the form of less improvement in liver stiffness measures (15).

The exact reasons for this finding have never been identified; however, we speculate that age-related alterations in the chest wall are involved. It is known that chest wall compliance decreases with age due to structural changes of the intercostal muscles,

intercostal joints and rib-vertebral articulations. In addition, age-associated osteoporosis may increase kyphosis, resulting in changes in the geometry of the thorax (16).

As previously reported, obesity was associated with a nearly threefold risk of poor response according to the fibroscan results in HCV patients (15).

This could be explained because subcutaneous and pre-hepatic adipose tissue in obese patients interferes with transmission of the mechanical shear wave and/or the measurement of its propagation by the FibroScan device. Another explanation was also suggested that high BMI (>35 kg/m2) has been associated with overestimation of fibrosis with the fibroscan probe compared to histologic assessment (17).

This study comes in agreement with another study which reported a negative correlation between HBA1C and FIB4 score before and after treatment (18).

Conclusion

Based on our findings, it is apparent that both HCV treatment regimens (Sofosbuvir + Daclatasvir ± Ribavirin as dual or triple therapy (for 12 weeks) and Sofosbuvir + Simeprevir ± Ribavirin as dual or triple therapy (for 12 weeks)) showed improvement in liver fibrosis, fibro scan parameters showed a significant decrease in both groups compared to the baseline. There was a significant negative correlation between fibro scan parameter decrease with age, BMI, and HbA1C levels. There was no difference in degree of improvement of liver fibrosis between both regimen (sofo. + simp.) (sofo. + dacla.)

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