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Changes in Liver Fibrosis as Determined by FIB-4 Score Following Sofosbuvir-Based Treatment Regimes Without Interferon

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A B S T R A C T

Objective: To determine the mean change in liver fibrosis as evaluated using the FIB-4 score following Sofosbuvir based treatment regimens without interferon.

Methodology: This prospective observational study was conducted at the Department of Medicine, Federal Government Services Hospital, Islamabad, from January 09, 2019 to January 03, 2020. A total of seventy (n=70) patients of either gender between age 18-75 years who were diagnosed with cases of HCV infection were enrolled in this study. All patients were treated with Sofosbuvir-based treatment regimens and were assessed for liver fibrosis using the FIB-4 score at baseline, at end of treatment (EOT) and 12 weeks after EOT.

Results: The mean FIB-4 score at baseline was 2.45±0.42, at EOT was 1.0981±0.33 and at 12 weeks after EOT was 1.51±0.32. As compared to the baseline, the mean FIB-4 score was significantly lesser at EOT (P=0.001) and at 12 weeks after EOT (P=0.001). A similar trend was observed across all stratified groups, i.e., age, gender, and type of patients (P<0.05 across all groups).

Conclusion: The sofosbuvir-based treatment regimen significantly reduced liver fibrosis at EOT and 12 weeks after EOT, as evidenced by FIB-4 scores that were significantly lower than baseline at EOT and 12 weeks after EOT.

Keywords: Transient Elastography (TE), Liver fibrosis, Sofosbuvir, Direct-acting antivirals (DAAs)

Introduction

Hepatitis C infection is one of the leading causes of chronic liver disease across the world.[1] Approximately 185 million people are chronically diseased around the world, although the majority are unaware of their condition.[2] HCV seroprevalence is around 6.7 percent in Pakistan, whereas adult viremic prevalence is 5.8 percent, making Pakistan the world's second-highest viremic infection country. In Pakistan, which has a population of 190 million people, an estimated 12.9 million people are infected with the hepatitis C virus.[3] With a chronicity rate of 55–85 percent, the vast majority of these people will develop cirrhosis and Hepatocellular Carcinoma unless they are properly recognized and treated.

The treatment of HCV has progressed recently with the introduction of direct-acting antiviral (DAA) medications, which were first used in clinical practice in 2014/2015. They revealed that HCV treatment has a bright future ahead of it, with greater SVR rates, shorter and simpler regimens, and fewer treatment-related side effects in HCV-infected individuals.[4]

For decades, the main issue of research and discussion in the community of hepatologists has been the progression of liver fibrosis. Recent research has shown that fibrosis

can be reversed in various chronic liver illnesses, including chronic viral hepatitis.[5] Several studies have found that utilizing powerful antiviral medications to treat chronic hepatitis C patients can reduce liver fibrosis by decreasing hepatic necroinflammation and reducing damage in sustained responders and slowing advancement in relapsers.[6,7]

Transient elastography (TE) has become the gold standard for non-invasive liver fibrosis assessment recently.[8] Moreover, various non-invasive laboratory techniques, such as the FIB-4 and APRI scores, are accurate in staging chronic liver disorders before antiviral treatment and in predicting hepatic fibrosis in HCV patients. Furthermore, these scores have been used to track chronic hepatitis patients over time and assess the effectiveness of antiviral therapy. Bachofner et al[9] recently concluded that Patients with SVR after Direct-acting antiviral therapy showed significant regression of TE values, which was in concordance with the regression of validated fibrosis scores FIB-4 and APRI at end of treatment and SVR12 using p value<0.001. The baseline FIB-4 score was 2.54 ± 0.605SD and at end of the treatment, it was 1.8 ± 0.4025SD. Considering the heavy burden of hepatitis C in Pakistan coupled with the fact that no such study has been reported from Pakistan reflecting the impact of DAAs on liver fibrosis, we felt prompted to conduct this study.

Methodology

This prospective observational study was conducted at the Department of Medicine, Federal Government Services Hospital, Islamabad from 01-09-2019 to 01-03-2020. The sample size was calculated using OpenEpi calculator with the statistical assumptions of 5% alpha error and 95% confidence interval taking mean FIB-4 score before the treatment as 2.54 ± 0.695 and after the treatment as 1.8 ± 0.4075.[8] The sample size was estimated to be at least 70 patients in the study. FIB-4 score was evaluated as follows:

$$FIB\text{-}4 = \frac{Age\ (years)\ \times\ AST\ (U/L)}{Platelet\ Count\ (10^9/L)\ \times\ \sqrt{ALT\ (U/L)}}$$

Degree of fibrosis was graded as minimal: FIB-4 < 1.45, moderate: FIB-4 1.45 - 3.25, and significant: FIB-4 > 3.25. All patients aged 18–75 years with PCR-positive HCV either treatment naive (A person who has never received any treatment for HCV) or experienced (A person who has received treatment previously for HCV

other than oral antivirals) was offered to enroll in the study. Those patients having either HBV or HIV coinfection, evidence of decompensated chronic liver disease, poorly controlled diabetes mellitus (HbA1C > 9%), and diagnosis of any malignancy whether hepatic or extrahepatic were excluded from the study.

Ethical approval was obtained from institutional ethical committee vide letter no. 1/2017-E/C-55. After the approval of synopsis, 70 consecutive cases of Chronic hepatitis C satisfying the inclusion and exclusion criteria were offered to enroll in the study. All patients were enrolled using a non-probability convenient sampling technique. The purpose of the study was explained in detail to all the patients and informed consent was taken in each case. Detailed clinical history, clinical examination and routine laboratory workup including CBC, LFTs and ultrasound were done for the patients. All patients were treated with Sofosbuvir-based regimens in accordance with EASL 2018 treatment guidelines. Accordingly, the patients were prescribed a combination of Sofosbuvir 400mg + Velpatasvir 100mg tablet once daily for 12 weeks. At week zero (baseline), EOT (end of therapy), and 12 weeks after EOT, patients were tested for HCV RNA. SVR12 was defined as undetectable HCV RNA by a quantitative polymerase chain reaction assay 12 weeks after EOT.FIB-4 score was calculated for each case at baseline, EOT and SVR12. All these variables were recorded in a predesigned proforma along with name, age, gender and Hospital ID of patient.

All the collected data was entered in SPSS version 21. The qualitative variables like gender, type of patient based on treatment, frequency and percentage and quantitative variables as age, Fib-4 score at baseline, the end of treatment and 12weeks after end of treatment be described as mean ± standard deviation and compared by paired sample t-test. Stratification analysis was done for variables such as age, gender, type of treatment received and a post-stratification paired sample t-test was done to allow for confounders.

Results

A total of seventy (n=70) patients of either gender between age 18–75 years who were diagnosed cases of HCV infection were enrolled in this study. Both treatment naïve and treatment-experienced patients were enrolled. All patients were treated with Sofosbuvir-based treatment regimens according to the approved treatment recommendation and were assessed for liver fibrosis

using FIB-4 score at baseline, at end of treatment (EOT) and at 12 weeks after EOT. The mean FIB-4 score at baseline was 2.45±0.42, at EOT was 1.0981±0.33 and at 12 weeks after EOT was 1.51±0.32 (Table I). compared to the baseline, the mean FIB-4 score was significantly lesser at EOT (P=0.001) and at 12 weeks after EOT (P=0.001). Data were further stratified for age (Table II), gender (Table III) and type of patient (Table IV). Similar trend was observed across all stratified groups and compared to the baseline, the mean FIB-4 score was significantly lesser at EOT and at 12 weeks after EOT (P<0.05 across all groups).

Table I: Comparison of Mean FIB-4 score at different time intervals

Time	Mean Fib-4 Score	Std. Deviation	P-Value t-test
Baseline	2.42	0.40	0.001
EOT	1.98	0.33	
Baseline	2.42	0.40	0.001
12 weeks after EOT	1.51	0.32	

Table II: Comparison of Mean FIB-4 score at different time intervals (stratification for age)

Age groups	Time	Mean Fib-4 score	Std. Dev	P-Value t-test
18-46 years	Baseline	2.37	0.42	0.002
	EOT	2.01	0.35	
	Baseline	2.37	0.42	0.001
	12 weeks after EOT	1.54	0.31	
47-75 Years	Baseline	2.46	0.38	0.001
	EOT	1.97	0.32	
	Baseline	2.46	0.38	0.001
	12 weeks after EOT	1.49	0.33	

Discussion

The chronic viral hepatitis C infection causes liver fibrosis, eventually leading to cirrhosis. To determine prognosis and treatment options, a fibrosis assessment is required. Patients undergoing direct-acting antiviral (DAA) therapy for hepatitis C exhibited considerable improvement in fibrosis scores (FIB-4), according to research. Several studies published in the literature have shown that administering potent antiviral medications can reverse fibrosis in people with chronic viral hepatitis.[5-7]

Table III: Comparison of Mean FIB-4 score at different time intervals (stratification for gender)

Gender	Time	Mean Fib-4 score	Sad. Dev	P-Value t-test
Males	Baseline	2.37	0.39	0.001
	EOT	1.95	0.33	
	Baseline	2.37	0.39	0.001
	12 weeks after EOT	1.45	0.31	
Females	Baseline	2.51	0.39	0.003
	EOT	2.04	0.32	
	Baseline	2.51	0.39	0.001
	12 weeks after EOT	1.59	0.33	

Table IV: Comparison of Mean FIB-4 score at different time intervals (stratification for type of patients)

Patient Type	Time	Mean Fib-4 score	Std. Dev	P-value T-test
Treatment Naive	Baseline	2.45	0.42	0.002
	EOT	2.01	0.35	
	Baseline	2.45	0.42	0.001
	12 weeks after EOT	1.52	0.34	
Treatment Experienced	Baseline	2.38	0.35	0.001
	EOT	1.93	0.28	
	Baseline	2.38	0.35	0.001
	12 weeks after EOT	1.49	0.28	

Non-invasive laboratory approaches such as the FIB-4 and APRI scores have been utilized to accurately stage chronic liver disorders before antiviral therapy and predict hepatic fibrosis in HCV patients. This study was planned to prospectively determine the mean change in Liver fibrosis as evaluated using FIB-4 score following Sofosbuvir based treatment regimens without Interferon. Our results showed that the mean FIB-4 score at baseline was 2.45±0.42, at EOT was 1.0981±0.33 and at 12 weeks after EOT was 1.51±0.32. compared to the baseline, the mean FIB-4 score was significantly lesser at EOT (P=0.001) and at 12 weeks after EOT (P=0.001). A similar trend was observed across all stratified groups, i.e., age, gender, and type of patient (P<0.05 across all groups).

The current study found that the mean FIB-4 score was significantly lower at EOT (P=0.001) and 12 weeks after

EOT (P=0.001) compared to the baseline. Our findings are comparable to that of Bachofner et al[8] who reported that Patients with SVR after direct-acting antiviral therapy demonstrated significant regression of TE values, which was in concordance with the regression of validated fibrosis scores FIB-4 and APRI at the conclusion of treatment and at 12 weeks after EOT (p value 0.001). Hsu WF et al[10] investigated how noninvasive fibrosis indicators and liver stiffness measurement (LSM) changed over time in individuals with chronic hepatitis C (CHC) who were using direct-acting antiviral drugs (DAAs). They reported that the median FIB-4 value fell from 2.88 (1.56–5.60) at baseline to 2.10 (1.30–3.65), 2.15 (1.30–3.65), 2.11 (1.37–3.76), and 2.22 (1.45–3.82) at week 2, week 4, end of therapy, and PW12 in patients who underwent DAA therapy and achieved SVR 12 weeks following therapy (n = 388). The authors concluded that in patients with chronic hepatitis C who achieved SVR to DAA therapy, the FIB-4 score decreased rapidly and steadily from week 2 to 12 weeks after treatment ended. The quick decrease in FIB-4 readings could be attributed to a decrease in necroinflammation. Stibbe KJM et al[11] examined seven non-invasive tests in chronic hepatitis patients, individually and in combination, to detect early stages of fibrosis based on the Metavir score in liver biopsy. They concluded that non-cirrhotic and cirrhotic patients may be successfully distinguished by HA, APRI, FibroTest, Fib-4, and TE. All tests, except the MBT, distinguish between mild and severe fibrosis. FibroTest, Fib-4, and TE were the most accurate single tests for detecting early fibrosis; however, incorporating multiple non-invasive tests increased the reliability for detecting liver fibrosis to such an extent that they could be used to substitute liver biopsy. Papadopoulos N et al[12] showed that the APRI/FIB-4 combination performed well in predicting significant fibrosis, while FIB-4 performed well in predicting cirrhosis.[2]

Several authors evaluated the diagnostic accuracy of FIB-4 score alone and compared with FibroTest, aspartate aminotransferase-platelet ratio index (APRI), or TE, with biopsy as a reference, in patients with chronic hepatitis C (CHC) or B (CHB). Houot M et al[13] included 71 studies including 77 groups according to etiology (All-CB) were eligible: 37 Only-C, 28 Only-B, and 12 Mixed-C-B. Their analysis revealed that in CHC and CHB, FIB-4 had better performances, than APRI and almost equivalent to TE for identifying advanced fibrosis in All-CB, without a significant difference for identifying cirrhosis in all

groups. Ragazzo TG et al[14] concluded that the most effective tool for assessing all degrees of fibrosis remained transient elastography. To clinically validate FIB-4, Vallet-Pichard A et al[15] compared the findings of 780 FIB-4 and FibroTests done on the same day in a group of 592 HCV-infected individuals. They found that the FIB-4 index is a straightforward, accurate, and economical approach for measuring liver fibrosis for values outside 1.45–3.25, and that it was coherent with FibroTest results. In a retrospective study of 711 chronic HCV patients, Li X et al[16] looked at the predictive capability of four blood indices: the fibrosis index based on four factors (FIB-4), the aspartate aminotransferase-to-platelet count ratio index (APRI), the aspartate aminotransferase-to-alanine aminotransferase ratio (AAR), and the gamma-glutamyl transpeptidase (GPR). They found that FIB-4's diagnostic performance (area under curve, AUC: 0.961) was better than APRI, AAR, and GPR's (AUC: 0.636, 0.746, and 0.661, respectively) for HCC prediction. In the prediction of cirrhotic patients, FIB-4 outperformed other indices, with an AUC of 0.775 compared to other scores ranging from 0.597 to 0.671.

In conclusion, while liver biopsy result is the gold standard for identifying the severity of liver fibrosis, concerns about its invasiveness and the tiny volume of liver tissue analysed restrict its usefulness and interpretation in medical practice. Some of these limitations can be addressed with non-invasive liver fibrosis evaluation approaches. Non-cirrhotic and cirrhotic patients can be successfully distinguished by HA, APRI, FibroTest, Fib-4, and TE. FibroTest, Fib-4, and TE were the most accurate single tests for detecting early fibrosis. Combining several non-invasive tests improved the accuracy of detecting liver fibrosis to the point where it may be used instead of liver biopsy. The current study has certain limitations. To begin with, we believe the sample size was somewhat small yet adequate for drawing the inference. Second, we did not compare our findings to those obtained using other techniques such as fibroscan or transient elastography. Future studies with bigger sample size and a mix of non-invasive methods to measure liver fibrosis in individuals who will be treated with direct antiviral medicines are recommended.

Conclusion

Sofosbuvir based treatment regimen significantly reduced liver fibrosis at EOT and at 12 weeks after EOT, as

evident on FIB-4 scores at EOT and 12 weeks after EOT, which were significantly lesser from baseline.

We recommend future studies with larger sample size and considering a combination of non-invasive modalities to assess liver fibrosis in patients planned for treatment with direct antiviral agents.

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