The Impact of a Sustained Virologic Response to Hepatitis C Virus Treatment on Liver Stiffness in the Puerto Rico Veterans Attending Liver Clinics in the Veterans Affairs Caribbean Healthcare System

Andres Rabell-Bernal, MD; Ricardo López-Valle, MD; Angel Morales-Santiago, MD; Doris H. Toro, MD, FACG, AGAF, FACP

Objective: To evaluate the impact of sustained virologic response (SVR) on liver stiffness, as measured by transient elastography (TE), in Hispanic patients treated with direct-acting antivirals (DAAs) in the outpatient clinics in the Veterans Affairs Caribbean Healthcare System.

Methods: We included hepatitis C virus (HCV) patients treated with DAA regimens from 11/2017 through 06/2019. Patient demographics and variables such as body mass index, HCV genotype, and treatment regimen were collected. The patients had a TE measurement before treatment initiation, and a repeat study 6 to 9 months after the achievement of SVR. A comparison between pre and post-treatment TE scores was performed via a paired t test.

Results: Forty-three subjects met all the inclusion criteria and completed a post-treatment TE. Most of the subjects were infected with genotypes 1a or 1b. Six to 9 months post SVR, we measured liver stiffness and found a statistically significant reduction in TE score (P value = .0003). The pretreatment median TE score was 10.2 kPa. On a repeat TE study at 6 to 9 months post-treatment, our subjects had a median score of 7.2 kPa.

Conclusion: The eradication of HCV infection with DAAs is associated with improved TE scores. Fibrosis-stage reduction was more frequent in those who had stage 4 fibrosis prior to treatment. These results suggest that achieving SVR may spare patients from future clinical decompensation and complications. Adequate screening of this potentially deadly chronic infection can lead to early therapy with DAAs and the significant regression of fibrosis in this kind of patient.
[*P R Health Sci J 2022;41(3):123-127*]

Key words: Hepatitis C, Transient Elastography, Direct-Acting Antivirals, Sustained Virologic Response

Chronic infection with hepatitis C virus (HCV) occurs in 50 to 85% of patients who acquire this single-stranded RNA virus (1). Untreated HCV infection can, ultimately, result in cirrhosis, hepatocellular carcinoma, and the need for a liver transplant. One essential component in the evaluation of a patient prior to HCV treatment is the identification and staging of hepatic fibrosis as a given individual's fibrosis stage guides therapy and is also a key factor in determining the urgency of treatment. Previously, patients had to undergo a liver biopsy in order to stage their hepatic fibrosis. Determining fibrosis is now more easily achieved with noninvasive techniques such as ultrasound-based transient elastography (TE). The eradication of chronic HCV is ultimately associated with significant reductions in morbidity and mortality, particularly in those with advanced fibrosis (2).

Fortunately, there are various therapeutic alternatives available that can eradicate HCV. Multiple studies have reported that patients achieving a sustained virologic response (SVR) with IFN-based regimens can have a histological regression of liver fibrosis (3,4). The mechanism via which fibrosis regresses is not fully understood, but current evidence suggests that it is in part due to the reversion of hepatic stellate cells to a quiescent phenotype and to their elimination via apoptosis (5). With the introduction of more novel therapies in the form of direct-acting antiviral (DAA) agents, the treatment of HCV is now much more effective, safer, and better tolerated by patients compared to the INF-based regimens of the past. These drugs

Gastroenterology Section, VA Caribbean Healthcare System, San Juan, Puerto Rico

The authors have no conflict of interest to disclose.

Address correspondence to: Andres Rabell Bernal, MD, Gastroenterology Department, VA Caribbean Healthcare System, 10 Casia Street, San Juan, Puerto Rico 00921. Email: andres.rabell-bernal@va.gov

have revolutionized HCV therapy and are now the treatment of choice for most HCV-infected patients.

Based on previous studies, it is known that while liver fibrosis may regress in a patient after SVR, repair is frequently incomplete and cirrhosis persists in about 40% of the patients who had cirrhosis prior to treatment (6). This regression is likely not linear and may be influenced by multiple factors, such as the amount and physical distribution of the fibrosis, environmental factors, and genetic factors (7). To this day, there are limited data regarding the effect of DAAs on liver fibrosis following SVR. Should further evidence of fibrosis regression and its beneficial impact on patient prognosis emerge, treatment with DAAs may become more widely available and economically accessible.

Patients and Methods

This prospective study was conducted at the Veterans Affairs Caribbean Healthcare System (VACHS) hepatology clinics in San Juan, Puerto Rico. This study was approved by the Institutional Review Board (IRB) of the VACHS.

Hispanic patients with chronic HCV infection who were treated with IFN-free, DAA regimens from November 2017 through June 2019 and who had had a TE measurement before treatment initiation were assessed for inclusion in this study.

The HCV infection of a given patient was considered to be eradicated if, by 12 weeks post-completion of therapy, the patient experienced an SVR. FibroScan (Echosens, Paris, France), a noninvasive method for determining liver health, was used for all TE measurements.

Population

Subjects included in this study had to meet the following inclusion criteria: be 21–79 years old, be veterans (and patients of the VACHS) with a diagnosis of chronic hepatitis C who had been treated with DAAs and who had had a pretreatment baseline measure (ascertained using FibroScan) of liver stiffness, and be Hispanic or have Latino ethnicity (either or both being documented on a given patient's chart).

Subjects were excluded from the study if they were co-infected with HIV or HBV, were decompensated because of their liver disease, had any co-existing cause of chronic liver disease (i.e., autoimmune hepatitis, Wilson's disease, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis), were younger than 21 years old or were 80 years old or older, or had a body mass index (BMI) of 35 or greater, were non-Hispanic; subjects were also excluded if their liver stiffness had not been measured prior to treatment with a DAA.

Methodology

Authorized investigators screened the electronic medical records of VACHS HCV patients in order to identify potential candidates. Face-to-face appointments were then arranged. When a potential candidate showed up for his or her scheduled appointment, the individual was invited to participate in the study. The study was explained in detail, and all the questions said individual had were answered. When a candidate agreed to participate, the informed consent document and HIPAA authorization were obtained by the investigator. Follow-up of the enrolled subjects consisted of the collection of data from each person's electronic medical record.

The following information was included in the study: age, sex, BMI, cirrhosis status, genotype (1–6), whether the individual was treatment naive or had experience with DAAs, measurements (using FibroScan) of liver stiffness (pretreatment and at from 6 to 9 months post-SVR in kPa), fibrosis stage (1–4), and whether or not the candidate consumed significant quantities of alcohol (with the threshold for "significant" being defined for women as the consumption of more than 1 beer [or the equivalent in other forms of alcohol] per day and for men as the consumption of more than 2 beers [or the equivalent in other forms of alcohol] per day). On each participant's record, the presence of cirrhosis was noted with a "Yes" (with a "No" indicating no fibrosis) when disease was present; cirrhosis status was determined based on the following: the fibrosis-4 score, the aspartate aminotransferase-to-platelet ratio index, a liver imaging study, the FibroScan results, and/or a liver biopsy.

The FibroScan score ranges used to define each subject's fibrosis stage were from 2 to 8 kPa for stage 1 (F1 = mild fibrosis), from 8 to 9 kPa for stage 2 (F2 = moderate fibrosis), from 9 to 14 kPa for stage 3 (F3 = severe fibrosis), and from 14 kPa and up for stage 4 (F4 = fibrosis consistent with cirrhosis).

A number was assigned to each participant. All the patient data were stored in a password-protected electronic file, and paper documents were stored in the research offices of the VACHS.

Statistical analysis

The data obtained in this study underwent a descriptive analysis. Frequency and percentage distributions of categorical and quantitative variables were performed on the data of our patient cohort. The statistical program SPSS, version 13.0, was employed to calculate all the measurements. We utilized a paired t test and lock transformation to normalize the data.

Results

Of the 69 patients evaluated, 43 met the inclusion criteria and were able to complete their post-treatment TE. These subjects were males with a mean age of 65.3 (± 5.5) years. The majority of the subjects had BMIs of 25 to 29.9 kg/m2 (n = 18; 41.8%). Additionally, most of the patients (n = 39; 90.7%) did not have a previous history of significant alcohol use, which was defined (for males) as consuming more than 2 drinks a day.

The majority of the subjects were genotype 1a (n = 28; 65.1%) or 1b (n = 11; 25.6%) and were treatment naïve (n = 29; 67.4%). The most common DAAs used were sofosbuvir–ledipasvir (Harvoni®) (n = 16; 37.2%), elbasvir–grazoprevir (Zepatier®) (n = 12; 27.9%), and glecaprevir–pibrentasvir (Mavyret®) (n = 8; 18.6%). Refer to Table 1 for further details.

Table 1. Patient demographics

Variable	N = 43
Age (years)	
Mean ± SD	65.3 ± 5.5
Median	65
Range	55–79
Gender (%)	
Male	100
Female	0
BMI (n)*	
15–24.9 (kg/m^2)	17
25–29.9 (kg/m^2)	18
30–34.9 (kg/m^2)	8
35+ (kg/m^2)	0
Alcohol history (%)	
Yes	9.3
No	90.7
Genotype (n)	
1a	28
1b	11
2a or 2c	3
4	1
Cirrhosis (%)	
Yes	48.8
No	51.2
Previous treatment (n)	
Naïve	29
Experienced	14
Treatment (%)	
Sofosbuvir + velpatasvir (Epclusa®)	9.3
Sofosbuvir + ledipasvir (Harvoni®)	37.2
Glecaprevir + pibrentasvir (Mavyret®)	18.6
Paritaprevir + ritonavir + ombitasvir + dasabuvir (Viekira®)	2.3
Sofosbuvir + velpatasvir + voxilaprevir (Vosevi®)	4.7
Elbasvir + grazoprevir (Zepatier®)	27.9

*BMI: body mass index

The pretreatment median TE score was 10.2 kPa, with the scores falling in the range of from 4.3 kPa to 34.3 kPa. After a repeat TE study at 6 to 9 months post-treatment, our subjects had a median score of 7.2 kPa, ranging from 4.3 kPa to 15.4 kPa. This difference is statistically significant (P value= .0003). Although a small number of outlier values were seen on both the pretreatment and post-treatment TE studies, the majority of the data fell within the described ranges. Refer to Figure 1.

Prior to commencing treatment with DAAs, we analyzed the fibrosis stage of each patient, using that patient's TE scores; we determined that 27.9% (n = 12) had F1, 14% (n = 6) had F2, 23.3% (n = 10) had F3, and 34.9% (n = 15) had F4 consistent with cirrhosis. On comparing the post-treatment (6 to 9 months after reaching SVR) TE scores, we observed decreases in fibrosis stage in 20.9% (n = 9) of the patients with F4, in 7.0% (n = 3) of the patients with F3, and in 9.3% (n = 4) of the patients with F2. Contrarily, we observed a 37.2% (n = 16) increase of the patients with F1. In summary, 58% (n = 25) of the subjects had advanced fibrosis (F3–F4) at the pretreatment stage. After treatment, only 30% (n = 13) of the subjects with advanced fibrosis (F3–F4) remained at their pretreatment stage. Refer to Figure 2.

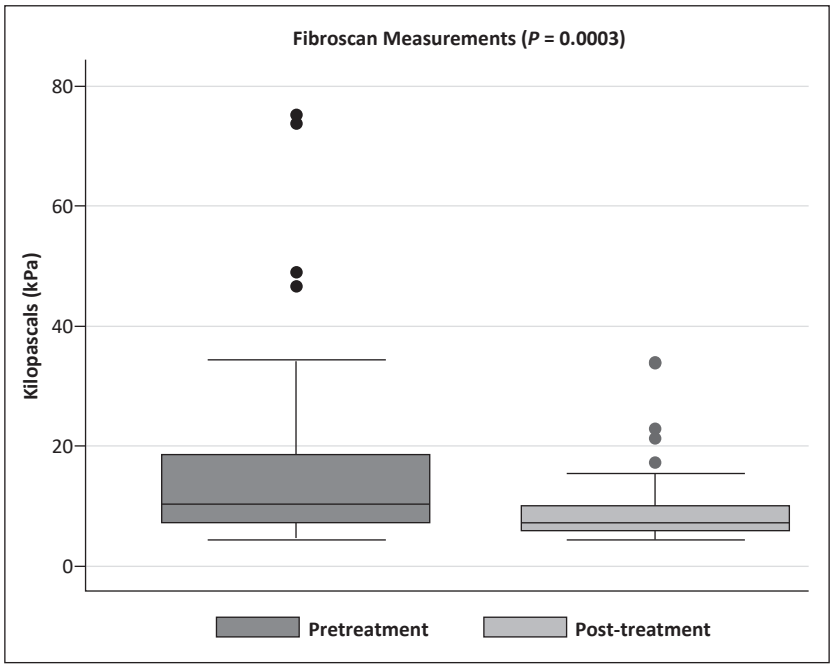

Figure 1. Pretreatment and Post-treatment Transient Elastography scores

Discussion

The ultimate goal of HCV treatment is to prevent long-term complications and improve long-term morbidity and mortality. The demonstrated improvement in liver stiffness after the successful eradication of the HCV infection is the first step in that direction. Our study results are consistent with those of previous studies that have shown similar findings (8–13). The reversal of fibrosis has also been demonstrated in patients with HCV who were treated with IFN-based therapies (14–19).

The achievement of SVR after the treatment of HCV not only promotes a measurable reduction in fibrosis but also has been proven to improve patient outcomes, which, ultimately, leads to reduced patient morbidity and mortality (15,20,21). It has also been evidenced that patients with and without esophageal varices who achieve SVR have a reduced probability of developing future liver decompensation events (22,23). Improvements in Model for End-Stage Liver Disease and Child–Pugh scores have also been evidenced in patients who have reached SVR after the completion of HCV treatment (9,13,24,25).

The eradication of chronic HCV with DAAs is clearly associated with improved TE scores. Fibrosis stage reduction was more frequent among those with pretreatment F4. Most

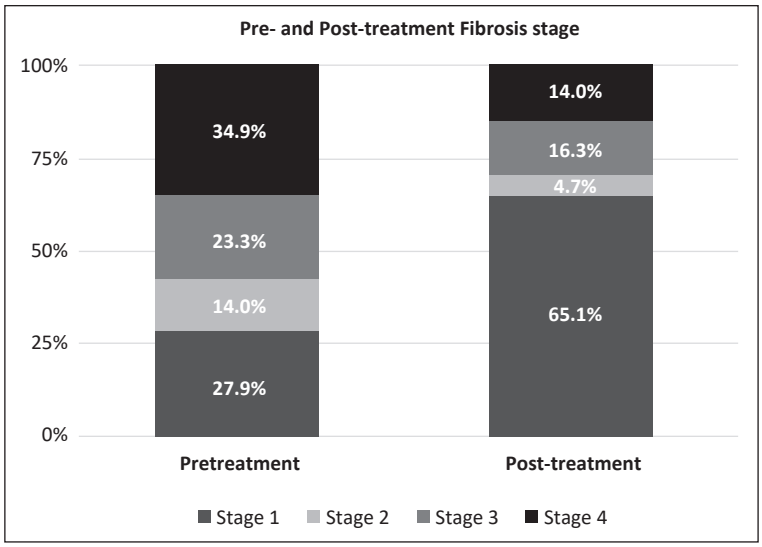

Figure 2. Pretreatment and Post-treatment Fibrosis stage

subjects with F4, who are prone to significant complications such as variceal bleeding, hepatic encephalopathy, ascites, hepatorenal syndrome, and malignancy, may be spared from these complications if successfully treated. Additional long-term studies are needed to verify whether the noted changes in TE scores are due to a reduction in inflammation or an actual reduction in hepatic fibrosis.

In our study, only 3 subjects had a minimal increase in their post-SVR TE scores. Of these 3 subjects, 1 was overweight and 1 was obese. It is likely that the presence in these patients of a concomitant liver disease, such as non-alcoholic fatty liver disease (NAFLD), significantly contributed to this mild increase in TE score (26–27). A recent consensus statement proposes a new definition for metabolic dysfunction–associated fatty liver disease. This group of experts recognized the disease resulting from metabolic-associated dysfunction as a separate entity contributing to significant liver disease in patients with or without co-existing conditions; the previously mentioned 3 patients might, in fact, suffer from this recently defined form of disease (28–29).

We must acknowledge that, although our results are statistically significant, our study is limited by both its small sample size and its lack of female representation. Consequently, our data cannot be definitively extrapolated to the general veteran population of Puerto Rico but only to the male veteran population on the island.

This study highlights the importance of eradicating chronic hepatitis C infection, regardless of the stage of fibrosis. The United States Preventive Task Force (USPSTF) currently recommends that adults aged 18 to 79 years should have at least a 1-time screening for HCV. For individuals who are above the age of 80 and who are also considered to be high-risk individuals, such as intravenous drug users and those who have been exposed to contaminated blood products, the USPSTF also recommends periodic HCV screening (30). Adequate screening of this potentially deadly chronic infection can lead to early therapy with the current highly effective DAAs, resulting in the significant regression of fibrosis in most of these patients.

Resumen

Objetivos: Evaluar el impacto de una respuesta viral sostenida (RVS) en la fibrosis hepática, según medida por elastografía, en pacientes de origen hispano que fueron tratados con antivirales de acción directa (AAD) en las clínicas de hígado del Hospital de Veteranos de San Juan. Métodos: Incluimos sujetos tratados para el virus de hepatitis C (VHC) con AAD entre 11/2017-06/2019. Se realizó una elastografía previo a el tratamiento y se repitió la misma luego de 6-9 meses de una RVS. Se compararon las medidas de elastografía pre y post-tratamiento utilizando la prueba-T-pareada. Resultados: Cuarenta y tres sujetos completaron el estudio. La mayoría tenía el genotipo 1a o 1b del VHC. Luego de medir la fibrosis hepática a los 6-9 meses de haber logrado una RVS, se demostró una reducción estadísticamente significativa en la puntuación de elastografía (p= 0.0003). La puntuación mediana de elastografía pre-tratamiento fue de 10.2 kPa. Al repetir la elastografía 6-9 meses post-tratamiento, los sujetos obtuvieron una puntuación mediana de 7.2 kPa. Conclusión: La erradicación de VHC con AAD está asociada con una mejoría significativa en la puntuación de elastografía. Una reducción en el estadío de fibrosis ocurrió con mayor frecuencia en sujetos que tenían fibrosis de estadío 4 previo a tratamiento. Estos resultados sugieren que alcanzar RVS pudiese prevenir futuras complicaciones y descompensación hepática. Un cernimiento adecuado de esta potencialmente letal infección puede dirigir a los pacientes a tratamiento temprano con AAD y de esta forma lograr una regresión significativa de fibrosis en la mayoría de los pacientes.

Acknowledgments

This research was conducted at the VA Caribbean Healthcare System, in San Juan, Puerto Rico, under direct supervision of principal investigator, Dr. Doris H. Toro. This material is based upon work supported by The Gastroenterology Department and Department of Veterans Affairs, Caribbean Healthcare System San Juan, P.R. Dr. Gerardo Jovet-Toledo performed the statistical analysis for this study. This work was supported by the Veterans Administration Caribbean Healthcare System in San Juan, Puerto Rico. We would like to extend our gratitude to the VA Caribbean Healthcare System Research and Development Service for its continuous support throughout the various stages of this study. We would also like to recognize Dr. Gerardo Jovet-Toledo, who performed the statistical analysis for this study. Additionally, we would like to thank our patients for their willingness to contribute in advancing the knowledge regarding

chronic hepatitis C infection. The contents of this manuscript do not represent the views of the Veterans Affairs Caribbean Healthcare System, the U.S. Department of Veterans Affairs, or the United States Government.

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