Direct-Acting Antiviral Therapy in Patients with Chronic Hepatitis C Shows Liver Fibrosis Regression on Three Noninvasive Tests: A Puerto Rican Cohort

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Objective: Direct-acting antiviral (DAA) drugs have resulted in high rates of virological cure in chronic hepatitis C (CHC)–infected patients. We used noninvasive tests to assess fibrosis in subjects who had been cured with DAA.

Methods: Retrospective data collection (2014-2019) from the medical record of CHC patients at the hepatology clinic was performed. Subjects co-infected with HIV and hepatitis B, post–liver transplant, and lost to follow-up were excluded. We evaluated fibrosis at baseline and 1 year after completing therapy using vibration-controlled transient elastography (VCTE), fibrosis-4 (FIB-4), and aspartate aminotransferase-to-platelet ratio index (APRI) scores.

Results: With 210 medical records reviewed, 41 were included. The mean age was 62.8 years; 61% were men. Significant fibrosis regression was observed 1 year post-treatment using 3 noninvasive methods: VCTE, APRI, and FIB-4 score. Prior to treatment, 46% of the patients had advanced fibrosis compared to 25% 1 year after treatment. The VCTE scores of 4 subjects (with body mass indices [BMIs] > 30) indicated a worsening of fibrosis. We did not find a statistically significant association between BMI and VCTE, FIB-4, or APRI score.

Conclusion: In most CHC patients, DAA therapy leads to liver fibrosis regression. Obesity may play an important role in the worsening of hepatic fibrosis or the absence of fibrosis regression.

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Key words: Chronic hepatitis C, Liver fibrosis, DAA, Noninvasive test, Regression

Chronic hepatitis C (CHC) is one of the leading causes of morbidity and mortality, worldwide, with a global prevalence of more than 150 million patients affected by this viral infection (1). In the United States, it is the primary condition identified as necessitating a liver transplant (2). If not treated, patients affected with this condition will go on to develop complications such as cirrhosis, portal hypertension, and hepatocellular carcinoma which represent the major causes of death in this population (3). Thus, in comparison with the general population, patients with CHC have a decreased life expectancy, which is mostly in part due to the high level of morbidity associated with this chronic disease (4). In Puerto Rico, CHC infection represents a public threat and a major economic burden, especially with its high prevalence in intravenous drug users (5).

Direct-acting antiviral (DAA) therapy is a newly available option for treatment of CHC infection; 95% of patients who undergo and complete this therapy achieve a sustained viral response (SVR) and are, in effect, cured, in that they show no virological evidence of active infection (6). The SVR is associated with improved intrahepatic and extrahepatic manifestations of CHC. This therapy, DAA, revolutionized the medical management of CHC to such a degree that, in 2016, the World Health Organization proposed a strategy that would make use of DAA to eradicate the hepatitis C virus (HCV) by 2030 (6). The introduction of an interferon alfa-free regimen has opened the opportunity to treat patients with decompensated chronic liver disease or prior liver transplantation (7). The liver fibrosis stage of a prospective patient must be evaluated prior to his or her starting therapy with DAA to determine the duration of treatment and assess the patient for signs of HCC once an SVR is achieved (8). Evaluation is often made noninvasively, using the aspartate aminotransferase-to-platelet ratio index (APRI) score, the fibrosis-4 (FIB-4) score, and vibration-controlled transient elastography (VCTE). Of patients who achieve an SVR, there is still a small but important number who fail to develop significant hepatic fibrosis regression after obtaining a virological cure (9). Thus, it is imperative to address factors that might increase morbidity and mortality in patients with CHC. To our knowledge, there are no available data on which factors are associated with poor outcomes in CHC patients from Puerto Rico. In this study, we aimed to describe hepatic fibrosis regression in Puerto Rican patients treated with DAA therapy. We planned to assess liver fibrosis regression in a noninvasive manner using APRI and FIB-4 scores along with VCTE, all replacing the more standard liver biopsy. A second objective was to determine what characteristics are associated with significantly decreased hepatic fibrosis regression in this population.

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Materials and Methods

Study population and data collection

Retrospective data were collected from the medical records of patients with a prior history of CHC who had achieved an SVR with a DAA regimen and had undergone VCTE, both before therapy and 1 year after therapy completion. The data were collected from January 2014 through December 2019 at a gastroenterology–hepatology center located in the southern region of Puerto Rico. An SVR was defined as an undetectable HCV RNA viral load at least 12 weeks after the completion of DAA therapy. Patients co-infected with HIV and the hepatitis B virus, who were lost to follow-up, and who did not achieve an SVR were excluded from this study. Hepatic fibrosis was assessed using VCTE (kPa) (FibroScan), FIB-4, and APRI scores, both before DAA therapy and after achieving an SVR. The VCTE stages were defined as follows: F0-F1 (≤ 7 kPa), F2 (7.1–9.4 kPa), F3 (9.5–12.4 kPa), and F4 (≥ 12.5 kPa). For each patient, the APRI score was calculated using the following formula: [(AST in IU/L) / (AST Upper Limit of Normal in IU/L) / (Platelets in 10^3/μL)]. The FIB-4 score was determined using the following formula: [(age in years x AST in IU/L) / (PLT in 10^3/μL x ($\sqrt{(ALT}$)in U/L)]. The upper limit of normal for both ALT and AST was 40 IU/L. Before therapy, clinical data and laboratory markers (age, sex, body mass index [BMI], viral load, genotype, α-fetoprotein [AFP] level, liver enzymes, international normalized ratio, hemoglobin level, platelet count, albumin, creatinine, fasting glycemia, and prior history of liver disease decompensation) were evaluated. The study was approved by the Institutional Board Review of Ponce Health Sciences University.

Results

Forty-one patients with CHC who were treated with a DAA regimen were selected for this study. Eighty-three percent of the subjects were treatment naïve, and all of them achieved an SVR with DAA. The mean age was 62.8 (±1.08) years, 61% were men (25/41), and the most frequent genotype was 1a (46%). The clinical characteristics are presented in Table 1. There was a balanced distribution of subjects at different stages of fibrosis (as measured by VCTE), with 34% at F0-F1, 20% at F2, 22% at F3, and 24% at F4; a higher proportion of subjects had indeterminate fibrosis per the FIB-4 and APRI scores (51% for both).

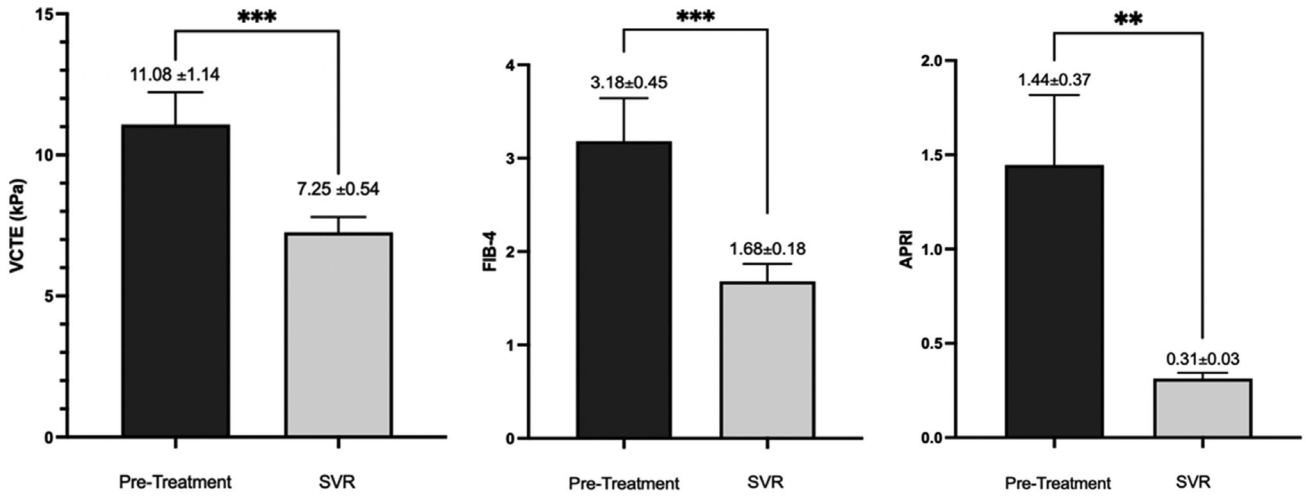
The response to fibrosis regression after therapy was characterized using the same noninvasive measurements (VCTE score, APRI score, and FIB-4 score). Data regarding each patient's liver fibrosis were recorded at 2 moments in time: at baseline (before therapy) and 1 year after therapy completion. Regression was defined as the reduction of the fibrosis score by at least 1 stage from baseline to follow-up. (Table 2). There were clinical improvements in the post-treatment results for at least 75% of the sampled patients. On average, these levels were improved to -3.8 (VCTE), -1.1 (APRI), and -1.5 (FIB-4). The regressions reached statistical significance ($P < .001$, .003, and .001, respectively) (Figure 1). Normal distribution was confirmed for all the quantitative variables by the Kolmogorov–Smirnov test.

Table 1. Baseline characteristics, Demographics, and Laboratory parameters of Subjects

Variable	Total cohort (N = 41)
Age, years (mean ± SEM)	62.8 ± 1.08
Sex, n (%)	
Male	25 (61%)
Female	16 (39%)
BMI (mean ± SEM)	28.1 ± 0.65 (n = 40)
AST (U/L), median (range)	52 (20–1302)
ALT (U/L), median (range)	73 (16–801)
ALP (IU/L), median (range)	83.5 (37–251)
Total bilirubin (mg/dl), median (range)	0.7 (0.2–4.7)
Albumin (g/dl), median (range)	3.9 (2.7–4.6)
Hemoglobin (g/dl), median (range)	14.5 (11–17)
Platelet count (x103/uL), median (range)	170 (49–377)
INR, median (range)	1.02 (0.87–1.57)
AFP (ng/mL), median (range)	4.17 (0.82–48.2)
Fasting glycemia, median (range)	101 (70–238)
Creatinine (mg/dl), median (range)	0.88 (0.56–2.35)
History of esophageal varices, n (%)	3 (7%)
Genotype	
1a	19 (46%)
1b	6 (15%)
1c	2 (5%)
2b	5 (12%)
2c	1 (2%)
3a	1 (2%)
Other	7 (17%)
Fibrosis stage	
VCTE	
F0-F1 (≤ 7 kPa)	14 (34%)
F2 (7.1–9.4 kPa)	8 (20%)
F3 (9.5–12.4 kPa)	9 (22%)
F4 (≥ 12.5 kPa)	10 (24%)
FIB-4	
No fibrosis < 1.45	7 (17%)
Indeterminate 1.45–3.25	21 (51%)
Fibrosis > 3.25	13 (32%)
APRI	
No fibrosis < 0.5	13 (32%)
Indeterminate 0.5–1.5	21 (51%)
Fibrosis > 1.5	7 (17%)
Treatment naïve	34 (83%)
Treatment	
Ledipasvir- sofosbuvir	18 (44%)
Sofosbuvir-velpatasvir	9 (22%)
Glecaprevir-pibrentasvir	5 (12%)
Elbasvir-grazoprevir	2 (5%)
Sofosbuvir-ribavirin	3 (7%)
ledipasvir-sofosbuvir + ribavirin	1 (2%)
simeprevir-sofosbuvir	3 (7%)
Regional district of Puerto Rico	
Arecibo	2 (5%)
Mayagüez	9 (22%)
Ponce	24 (58%)
Other	6 (15%)

Abbreviations: AFP, α-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; INR, international normalized ratio; VCTE, vibration-controlled transient elastography

Figure 1. Liver fibrosis was significantly different before and after Direct-Acting Antiviral Therapy (DAA) Therapy, as determined by Vibration-Controlled Transient Elastography (VCTE), Fibrosis-4 (FIB-4), and Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) scores



Abbreviations: SVR, sustained viral response

One year after achieving an SVR, the fibrosis levels (as determined by VCTE) had improved by 1 stage in 32% of the subjects, by 2 stages in 10% of the subjects, and by 3 stages in 7% of the subjects. No changes were observed in 34% of the subjects (i.e., they remained at the F0-F1 stage after achieving an SVR). We found that 8 subjects who showed poor liver fibrosis regression on VCTE (i.e., they remained at the F3-F4 stage after obtaining an SVR) were relatively older (mean age: 66 years), had a fasting glycemia over 100 mg/dL (2/8), and had preexisting diabetes mellitus (5/8); the majority were overweight (7/8). Three subjects showed increased liver stiffness after achieving an SVR, and 2 of them received sofosbuvir–velpatasvir. All of them had a BMI greater than 30, and none of them had a prior history of alcohol abuse. No statistically significant correlation was found between BMI and liver stiffness in VCTE.

Interestingly, changes in APRI and FIB-4 scores before and after therapy were more substantial in subjects with advanced fibrosis, and the differences in the results reached statistical significance. Subjects with advanced liver fibrosis (F3-F4, according to VCTE) prior to treatment or high APRI and FIB-4 scores had lower PLT counts and increased AFP levels. Older people with high alkaline phosphatase levels at baseline were found, based on their FIB-4 scores, to have advanced liver fibrosis. In our cohort, all the subjects showed improvements in terms of liver enzymes, albumin level, and PLT count after DAA therapy. No correlation was found between a given subject's genotype and viral load and liver stiffness regression.

Discussion

Hepatitis C infection continues to be an important cause of advanced liver disease. The evaluation of fibrosis is crucial in establishing the prognosis for, management of, and surveillance for HCC, among other complications. The gold standard for fibrosis assessment remains the liver biopsy; however, over the

Table 2. Liver fibrosis regression after subjects achieved a Sustained Viral Response (SVR). Data are Mean ± Standard deviation

		Mean	Standard deviation	Minimum	1st Quantile	3rd Quantile	Maximum
VCTE (kPa)	Before therapy	11.1	7.3	4.2	6.7	12.2	40.3
	After therapy	7.3	3.5	3.3	4.6	8.7	18.4
	Regression	-3.8	6.2	-31.6	-5.4	-0.8	4.3
APRI	Before therapy	1.4	2.4	0.1	0.4	1.3	13.8
	After therapy	0.3	0.4	0.1	0.2	0.3	1.3
	Regression	-1.1	2.3	-13.7	-1.1	-0.2	0
FIB-4	Before therapy	3.2	2.9	1.0	1.5	3.5	15.9
	After therapy	1.7	1.2	0.8	1.0	1.9	8.4
	Regression	-1.5	2.2	-11.8	-1.5	-0.3	0.2

Table 3. Changes from Baseline to a Sustained Viral Response (SVR) in laboratory results, stratified by Fibrosis stage using Vibration-Controlled Transient Elastography (VCTE)

	Stage F0-F1		Stage F2		Stage F3-F4	
	Baseline	SVR	Baseline	SVR	Baseline	SVR
Platelet count (10^3µL)	217 (63.8)	231 (46.1)	170 (32.4)	205 (34.1)	150 (58.9)	157 (63.2)
AST (IU/L)	140 (336)	19.4 (4.39)	55.2 (38.0)	20.6 (6.63)	74.5 (44.0)	22.3 (7.28)
ALT (IU/L)	215 (401)	19.4 (5.37)	92.0 (82.3)	22.6 (9.21)	103 (74.1)	39.1 (28.7)
Total bilirubin (mg/dL)	3.80 (7.38)	0.522 (0.349)	0.712 (0.345)	0.748 (0.515)	0.845 (0.517)	0.687 (0.372)
ALP	93.3 (44.1)	69.2 (19.8)	83.8 (24.7)	71.1 (17.2)	93.1 (51.1)	80.6 (30.0)
Albumin	3.97 (0.510)	4.28 (0.485)	4.35 (0.250)	4.57 (0.292)	3.80 (0.365)	4.32 (0.396)

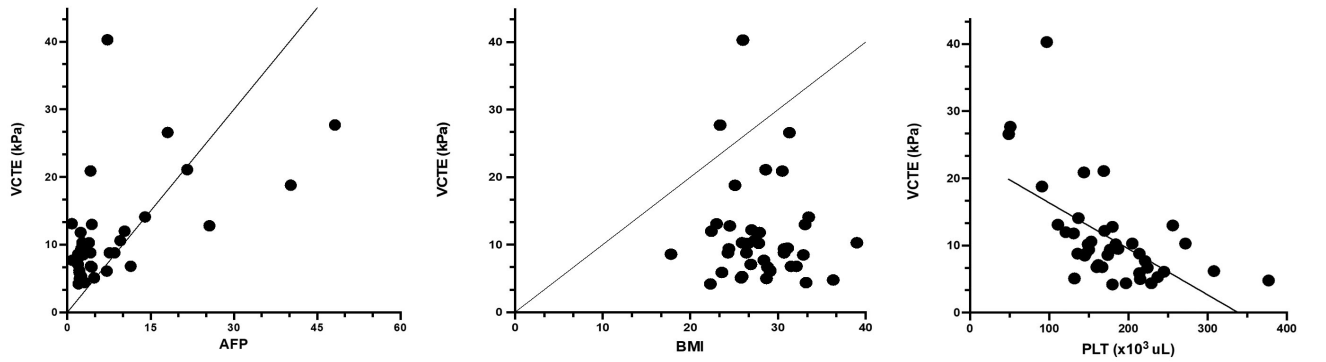
Data are means with standard deviations.

years, the characterization of fibrosis has shifted mostly to the use of noninvasive tests. To date, these new modalities have been shown to adequately reflect fibrosis regression. Despite not being as specific as a biopsy, they have been incorporated into the standard of care for the follow-up and management of patients with advanced liver disease. The most reliable noninvasive method for the assessment of liver fibrosis is VCTE (10). Fibrosis-4 and APRI scores are serological modalities that detect the presence and estimate the degree of liver scarring. Although these noninvasive tools provide reliable information about liver fibrosis, they may be confounded by an inflammatory response. Hence, an evaluation of fibrosis regression after HCV is (successfully) treated should be performed at some point after the patient achieves an SVR (11). Limited data in a Puerto Rican population is available regarding the accuracy of noninvasive assessments of liver fibrosis regression in CHC patients treated with DAAs. There are many patients in Puerto Rico with CHC and HCC, but the overall availability of medical resources is limited. That being the case, our study aimed to provide data on noninvasive liver fibrosis assessment tools used to better manage and provide follow-up for these patients.

All the subjects from our cohort received DAA treatment and achieved an SVR; 87% (37/41) showed fibrosis regression on VCTE, and all of them showed regression on APRI and FIB-4. Four subjects demonstrated worsening of liver fibrosis on VCTE, and all of them had a BMI greater than 30. Our liver clinic receives patients from all over Puerto Rico, and very often these patients are affected by multiple comorbidities, including diabetes mellitus, arterial hypertension, and dyslipidemia. It is known that diabetes mellitus and obesity are strongly associated with higher degrees of liver fibrosis and the worsening of outcomes (12–14); however, no statistically significant difference between glycemia and obesity and the degree of liver fibrosis was observed in our cohort. Increased age has been associated as a risk factor for poor liver fibrosis regression in patients, despite the receipt of DAA treatment (14). We observed that 12 out of 21 patients in our group who were 65 years old or older showed no change in fibrosis post-treatment. Five out of 21 were more than 70 years old, and of them, only 1 showed improvement of fibrosis. Poor regression in an older population, despite their having achieved an SVR, could be related to irreversible fibrosis caused by longer exposure to the virus.

A correlation between low PLT count and portal hypertension was observed. All 5 subjects with a VCTE score greater than 20kPa had a PLT count below 150 x 10^3 u/L, and 3 of them had evidence of esophageal varices on endoscopy. We observed that 34% of our cohort had thrombocytopenia (i.e., PLT count

Figure 2. Liver Stiffness (kPa) Correlations Were Significantly Associated with Level of α-Fetoprotein (AFP) and Platelet Count but Not with Increased Body Mass Index (BMI). Correlations Were Evaluated Using Pearson's Test.



P value = .0008
r: .5387

P value = .5708
r: -.0923

P value <.0001
r: -.5938

<150 x 10^3 u/L), which fell to 19% after SVR was achieved. These results are consistent with the effect of HCV on bone marrow suppression, severe liver fibrosis, and a subsequent decreased production of thrombopoietin and the autoimmune effect of HCV against platelets (15). We also observed higher levels of AFP in these same subjects. None of these subjects had a prior history of HCC or cholangiocarcinoma, but it would be interesting to see whether, in our population, there is an association between increased pre-treatment AFP levels and HCC risk after HCV DAA viral eradication, as has been reported in the literature (16).

Liver fibrosis regression after a DAA-induced SVR has been associated with decreased risks of liver decompensation, HCC, cardiovascular disease, and overall mortality (17). Eight subjects in our cohort did not show liver fibrosis regression, which was likely due to the short follow-up period (1 year). Knop et al showed that liver fibrosis regression continues years after viral eradication in a significant number of patients (18). We also need to highlight the possibility that the dramatic improvement of liver parameters observed in our population might have been related to the decreased inflammatory response after viral eradication and not necessarily to a decreased degree of fibrosis since regression occurs at a slower pace (19).

Our study has some disadvantages. First, it was a retrospective study, and the data were collected from a given patient's medical records during his or her first visit and follow-ups. Second, we had a small sample. A larger sample is needed to see whether to determine whether additional preventable and treatable factors that can potentially improve poor liver fibrosis regression exist. Third, we did not use liver biopsies before and after treatment to compare and confirm fibrosis degree against and with regard to VCTE, FIB-4, and APRI scores.

Despite our limitations, we were able to demonstrate, using 3 noninvasive methods, that viral eradication confers improvement in liver fibrosis, and this information supports the growing body of literature detailing the benefits that this novel therapy—DAA—confers on these patients. Such comorbidities, as obesity and diabetes mellitus, may play important roles in the poor regression of liver fibrosis, but a larger sample needs to be evaluated to determine a correlation between them.

Resumen

Objetivo: Los antivirales de acción directa (AAD) han demostrado un porcentaje alto en curación virológica en pacientes con hepatitis C crónica (HCC). Hasta donde sabemos, no existen datos sobre la regresión de la fibrosis hepática en pacientes puertorriqueños. Utilizamos pruebas no invasivas para evaluar la regresión de fibrosis en sujetos tratados con DAA que desarrollaron respuesta virológica sostenida (RVS). Métodos: Se hizo una recopilación retrospectiva de datos de pacientes con HCC en una clínica de Hepatología durante el 2014 al 2019. Se excluyeron sujetos coinfectados con VIH, Hepatitis B, trasplantados de hígado y que perdieron seguimiento. Evaluamos la fibrosis antes de AAD y al año después de completar terapia usando elastografía por ultrasonido (EUS), fibrosis-4 (Fib-4) e índice de aspartato amino transferase a plaquetas (APRI). Resultados: Se revisaron 210 expedientes médicos, de los cuales se incluyeron 41. La edad media fue 62.8 años, y 61% eran hombres. Se vio una regresión significativa de la fibrosis al año después de tratamiento en los 3 métodos no invasivos EUS, APRI y FIB-4. El 46% tenía fibrosis avanzada en comparación con el 25% al año después de la terapia. Cuatro sujetos mostraron empeoramiento en fibrosis en EUS y todos tenían un índice de masa corporal (IMC) mayor a 30. No se vió una relación estadísticamente significativa entre el IMC y EUS, FIB-4 o APRI. Conclusión: La cura de la hepatitis c crónica con AAD se asocia con regresión de fibrosis hepática en la mayoría de los pacientes. La obesidad puede tener un rol en el deterioro de la fibrosis hepática o en la usencia de su regresión.

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