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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Long-term Follow-up Liver Stiffness Results of Chronic Hepatitis C Patients Treated with Direct-acting Antivirals

Direkt Etkili Antivirallerle Tedavi Edilen Kronik Hepatit C Hastalarının Uzun Süreli Takiplerinde Karaciğer Sertliği Sonuçları

Gözde Derviş Hakim[1], Ayşe Gökçen Tufan[2]

[1]University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Gastroenterology, İzmir, Turkey
[2]Çiğli Education and Research Hospital, Clinic of Internal Medicine, İzmir, Turkey

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Abstract

Objective: Non-invasive assessments, i.e., transient elastography (Fibroscan®), FIB-4 (Fibrosis-4) and [AST (aspartate aminotransferase) to platelet ratio index] APRI scores are used to measure liver stiffness during the long term follow up of patients diagnosed with Chronic hepatitis C (CHC). To evaluate the liver stiffness measurements detected by non-invasive methods in CHC patients treated with direct acting antivirals (DAAs) in the long term.

Methods: Liver stiffness measurements carried out with transient elastography, FIB-4, APRI scores, and biochemical data before and after the treatment and during the long-term follow-up of 26 patients with CHC treated with DAAs were reviewed retrospectively. Patients receiving Paritaprevir + Ritonavir/Ombitasvir + Dasabuvir were included in group 1 (n=13), and patients receiving Sofosbuvir + Ledipasvir ± Ribavirin in group 2 (n=13).

Results: Mean liver stiffness measurement of the patients was 15.50±2.13 kPa (min-max: 5.20-45.00 kPa) before treatment, 12.15±1.84 kPa (min-max: 4.30-42.00 kPa) at the end of treatment and 9.73±1.57kPa (min-max: 3.0-42.2 kPa) at 28 months after the treatment. Significant regressions were also seen in the APRI and FIB-4 scores of patients during the long term follow up treatment compared to baseline (APRI at the onset of treatment: 0.79±0.62, APRI during the long term follow-up: 0.25±0.13, p<0.01; FIB-4 at the onset of treatment: 2.65±1.82, FIB-4 during the long term follow up: 1.66±1.23, p<0.01).

Conclusion: Significant improvements were seen in the stage of fibrosis in the long-term follow-up of the treatment with current antiviral therapies.

Keywords: Hepatitis C, direct-acting antiviral agents, fibroscan, APRI, fibrosis

Öz

Amaç: Non-invaziv değerlendirmeler, yani geçici elastografi (Fibroscan®), FIB-4 (Fibrozis-4) ve [AST (aspartat aminotransferaz) trombosit oran indeksi] APRI skorları, hastaların uzun süreli takibi sırasında kronik hepatit C (KHC) karaciğer sertliğini ölçmek için kullanılır. Direkt etkili antiviraller (DEA) ile tedavi edilen KHC hastalarında invazif olmayan yöntemlerle tespit edilen karaciğer sertliği ölçümlerini uzun dönemde değerlendirmek.

Yöntem: DAA ile tedavi edilen 26 KHC'li hastanın tedavi öncesi, tedavi sonrası ve uzun dönem izlemi sırasında transient elastografi, FIB-4, APRI skorları ve biyokimyasal veriler ile yapılan karaciğer sertliği ölçümleri retrospektif olarak incelendi. Paritaprevir + Ritonavir/Ombitasvir + Dasabuvir alan hastalar grup 1'e (n=13), Sofosbuvir + Ledipasvir ± Ribavirin alan hastalar grup 2'ye (n=13) dahil edildi.

Address for Correspondence/Yazışma Adresi: Gözde Derviş Hakim MD, University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Clinic of Gastroenterology, İzmir, Turkey
Phone: +90 505 266 31 38 **E-mail:** gozdedervis@gmail.com
ORCID ID: orcid.org/0000-0001-9676-9532

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Öz

Bulgular: Hastaların ortalama karaciğer sertliği ölçümü tedavi öncesi 15,50±2,13 kPa (min-maks: 5,20-45,00 kPa), tedavi bitiminde 12,15±1,84 kPa (min-maks: 4,30-42,00 kPa) ve tedaviden 28 ay sonra 9,73±1,57 kPa (min-maks: 3,0-42,2 kPa) idi. Tedavinin uzun dönem takibinde hastaların APRI ve FIB-4 skorlarında başlangıca göre anlamlı gerilemeler görüldü (tedavi başlangıcında APRI: 0,79±0,62, uzun dönem takipte APRI: 0,25±0,13, p<0,01; tedavi başlangıcında FIB-4: 2,65±1,82, uzun dönem takipte FIB-4: 1,66±1,23, p<0,01).

Sonuç: DEA ile tedavi edilen hastalarda, uzun dönem takiplerde fibrozis evresinde önemli düzelmeler olduğu görüldü.

Anahtar Kelimeler: Hepatit C, direkt etkili antiviral ajanlar, fibroscan, APRI, fibrozis

Introduction

Novel direct-acting antiviral (DAA) agents, which provide a significantly increased sustained virological response (SVR), aim to modify the natural course of the infection and prevent progression to hepatocellular carcinoma, thereby improving the quality of life and survival[1]. The stage of fibrosis is associated with the prognosis of Chronic hepatitis C (CHC) infection, and it is important for treatment decisions and monitoring of treatment[2]. Liver biopsy is accepted as the gold standard procedure for evaluating fibrosis; however, biopsy is an invasive method the accuracy of which may vary between observers and sampling errors may also occur[3]. These limitations result in a need for reliable, repeatable, and noninvasive methods for evaluating fibrosis[4].

A number of serological tests have been developed to detect liver fibrosis. Aspartate aminotransferase (AST)/platelet ratio index (APRI) and Fibrosis-4 index (FIB-4) are the most common biochemical markers used to evaluate fibrosis. However, the use of APRI and FIB-4 brings the risk of overestimation of the fibrosis stage due to the effect of necroinflammatory activity on transaminases[5]. Transient elastography (TE) is a method that measures the stiffness of the liver in numeric values and is considered an important tool to evaluate and monitor fibrosis as well as to determine the treatment of chronic liver diseases[6]. The combined use of serum markers and TE increases the accuracy of fibrosis evaluation[7-9]. This study aimed to evaluate liver stiffness measurements (LSMs) detected by Fibroscan® and APRI and FIB-4 scores for the long-term follow-up (LTFU) of patients diagnosed with CHC and treated by DAAs; evaluate the changes in fibrosis through noninvasive methods during the long-term; and to determine the effect of DAAs on these changes.

Materials and Methods

Patients

This study included 26 patients diagnosed with CHC whose liver stiffness was measured by Fibroscan 502 Touch (Echosens, Paris, France) during the LTFU of 40 patients, who were followed up at University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital, Department of Gastroenterology, completed DAA therapy for 12 to 24 weeks, developed SVR, and whose liver stiffness was measured by Fibroscan 502 Touch (Echosens, Paris, France) at the beginning and end of the treatment and during the LTFU.

Inclusion criteria:

1. Being over and at the age of 18 years,

2. Having a diagnosis of CHC and being treated with DAA agents,

3. Having analyses of biochemical parameters and Fibroscan LSMs before and after DAA treatment and during the LTFU.

Exclusion criteria:

1. Patients who discontinued DAA therapy,

2. Patients who have received DAA therapy had biochemical analyses and LSMs before and after the treatment, but failed to attend long-term control visits or died.

Fourteen of the 40 initially enrolled patients had to be excluded from the study at LTFU. It was determined that 3 of these 14 patients died, and 7 of them did not come to the hospital again due to distance, stating that they were well, and not wanting to come for control. Three patients could not be reached due to the phone number change.

The patients enrolled in the study were divided into 2 groups by including patients treated with Paritaprevir + Ritonavir/ Ombitasvir + Dasabuvir in group 1 (n=13) and patients treated with Sofosbuvir + Ledipasvir ± Ribavirin in group 2 (n=13). SVR; 12 weeks after treatment (SVR12) and/or 24 weeks (SVR24) after the end of treatment are conventionally used as CHC therapy endpoints. Approval for this study was obtained from the Ethics Committee of Clinical and Laboratory Research of University of Health Sciences Turkey,

İzmir Tepecik Education and Research Hospital with the number of 2020/8-25 (date: 08.07.2020).Verbal and written consent were obtained from patients participating in the study.

Data Collection

Age, gender, hepatitis C virus (HCV) genotype, cirrhosis status, and previous antiviral therapy for HCV were recorded in all patients. AST, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin, international normalized ratio (INR), serum creatinine, white blood cell (WBC), hemoglobin, and platelet levels of all patients enrolled in the study (n=26) measured before and after DAA therapy, and during the LTFU were recorded and reviewed retrospectively. Body mass index (BMI) of the patients was calculated according to the body weight/height^2 formula. LSMs detected by Fibroscan® and APRI and FIB-4 scores detected before and after the therapy and during the LTFU were recorded and reviewed.

Non-invasive Tests

LSMs were performed by the same experienced operator using Fibroscan® 502 Touch (Echosens, Paris, France) with M-probe. Liver stiffness was expressed in kPa, and the average value of 10 measurements performed with a depth of 25 to 65 mm was taken. Measurements with achievement rate (successful measurements x 100/all measurements) of at least 60% and measurements with IQR/M rate below 30% were accepted as valid and included in the statistical analysis. The cut off values of LSMs according to the METAVIR fibrosis stages were as follows[10-12]: F0-1: 2.5-7 kPA, F2: 7.1-9.5 kPA, F3: 9.5-12.5 kPA, F4: >12.5 kPA (F: fibrosis).

The following formulas were used for biochemical markers: APRI: (AST/upper limit of normal)/platelet count (expressed as platelets x 10^9/L) x100[11]. FIB-4: [age (years) x AST (IU/L)]/[platelet count (10^9/L) Ã— (ALT (IU/L) ½] (12).

Statistical Analysis

All study data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of numerical variables was tested for normality with the Shapiro-Wilk test. The pattern of change in variables in the three groups (pretreatment, posttreatment and LTFU) was examined using repeated-measures ANOVA. Cross tabulation was performed for categorical data, and chi-square and McNemar tests were used for the analysis. For numerical variables, Pearson's correlation coefficient was calculated for those with a normal distribution, and Spearman's rho correlation coefficient for those with nonnormal distribution. The level of statistical significance was a p value <0.05.

Results

Demographic and Clinical Characteristics

The mean age of the 26 patients enrolled in the study was 59.46±13.04 years; 34.6% of the participants were male, and 65.4% were female. The mean BMI of the patients was 28.07%±5.78 (Table 1). There was no significant difference between the treatment groups when the patients were evaluated according to the BMI in total and by each group (p=0.453) (Table 1). Sixteen patients (60%) were treatment-naive and 10 (40%) were not. While 13 patients were non-cirrhotic (50%), 13 (50%) had child A cirrhosis. Out of 13 patients in group 1 were 6 noncirrhotic (50%), 7 had child A cirrhosis (50%); in group 2, 7 patients were non-cirrhotic (50%) and 6 had child A cirrhosis (40%). There was no significant difference between the groups in terms of cirrhosis (p>0.05).

HCV Genotypes

When the HCV genotypes were analyzed, 23 of the 26 patients had genotype 1b (88.46%), 1 had genotype 2 (3.84%), and 2 had genotype 3 (7.70%). All the patients in group 1 had genotype 1b (100%), whereas 10 patients in group 2 had

Table 1. Demographics of patients

	Total patients	Group 1	Group 2	p-value
n	26	13	13	
Age	59.46±13.04	60.38±10.87	58.54±15.03	0.726
Gender M/F	9/17	5/8	4/9	0.680
Follow-up period (months)	27 (12-38)	27 (12-34)	28 (22-38)	0.367
BMI	28.07±5.78	26.47±4.01	27.73±4.36	0.453

n: Number, M: Male, F: Female, BMI: Body mass index

genotype 1b (76.90%), 1 had genotype 2 (7.70%), and 2 had genotype 3 (15.40%). There was no statistically significant difference between the groups regarding genotype distribution (p>0.05).

Laboratory Findings

The mean AST, ALT, GGT, INR, and platelet values of the patients measured before and after treatment and during the LTFU are provided in Table 2. There was a statistically significant decrease in AST (p<0.001), ALT (p=0.001), GGT p<0.001), and INR (p=0.037) levels during the LTFU compared with pre-treatment values. However, no superiority of any treatment group was detected in comparisons between the treatment groups. An elevation was noted in PLT values during the LTFU; however, this change was not statistically significant (p=0.055). There was an increase in platelet counts during the LTFU in both groups, although without a significant difference between the groups (p=0.226) (Table 2).

APRI Score

A significant regression was detected in APRI levels at the end of treatment and during the LTFU (p<0.01) (Table 3). A decrease was detected in APRI scores during the LTFU compared with baseline and post-treatment scores. The regression detected in APRI scores between pretreatment and LTFU values was statistically significant (p<0.01). However, the regression detected in APRI scores between post-treatment and LTFU values was not statistically significant (p=0.06). The APRI

Table 2. Mean values of laboratory findings in pretreatment, posttreatment and long-term follow-up analyses

	Total patients	Group 1	Group 2	p-value
n	26	13	13	
Platelets (x10³/µL)				
BT	207576±74697	224538±75785	19061±72510	0.055
AT	206432±82894	218557±97278	194307±67335	0.059
LTFU	236500±99772	260538±91035	212461±105826	0.226
INR				
BT	1.11±0.17	1.14±0.21	1.08±0.12	**0.037***
AT	1.11±0.17	1.10±0.20	1.12±0.14	0.327
LTFU	1.04±0.07	1.07±0.07	1.01±0.07	**0.035***
AST(UI/ML)				
BT	55.77±36.43	47.08±23.48	64.46±45.27	**<0.001***
AT	22.15±7.54	21.31±5.73	23.00±9.17	0.524
LTFU	20.35±4.46	20.00±4.43	20.69±4.64	0.701
ALT (UI/ML)				
BT	64.31±84.78	46.46±32.94	82.15±114.88	**0.001***
AT	16.46±9.47	16.23±8.97	16.69±10.31	0.330
LTFU	16.58±5.58	15.85±3.97	17.31±6.87	0.514
GGT (UI/ML)				
BT	75.65 ± 72.86	65.31± 56.14	86.00±87.61	**0.001***
AT	33.92 ± 33.25	35.15±42.01	32.69±23.15	0.732
LTFU	26.92 ± 13.02	27.38±12.30	26.46±14.20	0.861
Total bilirubin (mg/dL)				
BT	0.89±0.27	0.83±0.22	0.95±0.32	0.152
AT	0.75±0.36	0.82±0.70	0.68±0.22	0.251
LTFU	0.69±0.19	0.65±0.15	0.73±0.22	0.383

*There is a significant difference between groups

P: Comparison of pre and posttreatment and LTFU values between the treatment groups

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, INR: International normalized ratio, AT: After treatment (within 1 month after treatment), BT: Before treatment, LTFU: Long-term followup

score was found to be statistically similar when APRI score levels were compared between the treatment groups before and after the treatment as well as during the LTFU (p=0.550) (Table 4). Comparison of regression rates of APRI scores with the regression rate in other parameters revealed a strong positive correlation between the APRI score and AST, ALT, and FIB-4 in the baseline and post-treatment analyses (Table 5). A positive correlation was observed between the regression rates in AST, ALT, INR, and FIB-4, and the regression rates in APRI scores when baseline and LTFU results were compared (Table 6). A positive correlation was detected between the regression in APRI scores and the regressions in ALT and AST levels in post-treatment and LTFU results (p<0.001) (Table 7).

FIB-4 Scores

A significant regression was detected in FIB-4 levels at the end of treatment and during the LTFU (p<0.01) (Table 3). A decrease was detected in FIB-4 scores in the LTFU analyses compared with pre- and post-treatment analyses. The regression detected in FIB-4 values in the pretreatment and LTFU analyses was statistically significant (p<0.01). However, there was no statistically significant difference (p=0.119) in the regression detected in FIB-4 values in the post-treatment and LTFU analyses (Table 3). There was no statistically significant difference between the groups in terms of FIB-4 in the pre-treatment, post-treatment, and LTFU analyses (p=0.796) (Table 4). The regression rates in the FIB-4 score in the baseline and post-treatment analyses positively correlated the regression rates of AST and APRI scores (p<0.001, and a negative correlation was detected between the regression in the FIB-4 score and the increase in platelet count (p<0.05) (Table 5).

A positive correlation was observed between the regressions in FIB-4 scores and the APRI, AST, and ALT values in the baseline and LTFU analyses (p<0.001, p=0.007, p<0.001, respectively). A strongly positive correlation was detected between the AST and APRI scores (Table 6). In the post-treatment and LTFU comparisons, a positive correlation was detected between the regression in FIB-4 scores and the regression rates in AST values (p<0.037), whereas a negative correlation was found between the regression in FIB-4 scores and the increase in PLT values (p<0.001) (Table 7).

Liver Stiffness Measurements

The regression of LSMs was statistically significant (p=0.001, p=0.005) in the post-treatment and LTFU analyses (Table 3). When changes in the fibrosis stage were analyzed according to the pre-treatment and LTFU measurements of liver fibrosis, it was noted that 15.38% of the patients (n=4) had F0-1 fibrosis, 23.07% (n=6) had F2 fibrosis, 19.25% (n=5) had F3 fibrosis, and 42.30% (n=11) had F4 fibrosis before treatment. Five of the 11 patients who had F4 fibrosis before DAA treatment (45.45%) remained at F4, while 4 patients (36.36%) regressed to F3 and 2 patients (18.19%) regressed

Table 3. Comparison of mean APRI values, mean FIB-4 values, and LSM scores according to treatment duration

	BT	AT	LTFU	BT-AT	BT-LTFU	AT-LTFU
APRI total	0.79±0.62	0.312±0.195	0.25±0.13	<0.01*	<0.01*	0.060
FIB-4	2.65±1.82	1.89±1.18	1.66±1.23	<0.01*	<0.01*	0.119
LSMs	15.50±2.13	12.15±1.84	9.73±1.57	0.001*	0.005*	0.107

*There is a significant difference between groups. Mean ± SD

APRI: Aspartate aminotransferase (AST) / platelet ratio index, FIB-4: Fibrosis-4 index, LSMs: Liver stiffness measurement score, AT: After treatment (within 1 month after treatment), BT: Before treatment; LTFU: Long term followup, SD: Standard deviation

Table 4. Mean values of APRI scores, FIB-4 scores, and LSM scores according to treatment duration

	BT	AT	LTFU	p-value
APRI group 1	0.63±0.57	0.26±0.21	0.22±0.10	0.550
APRI group 2	0.95±0.66	0.36±0.17	0.29±0.15	-
FIB-4 group 1	2.30±1.57	1.66±1.09	1.36±0.73	0.796
FIB-4 group 2	3.00±2.04	2.11±1.26	1.95±1.57	-
LSMs group 1	13.76±7.67	10.65±6.23	8.20±3.56	0.946
LSMs group 2	17.24±13.48	13.64±11.84	11.26±10.76	-

Mean ± SD, APRI: Aspartate aminotransferase (AST)/platelet ratio index, FIB-4: Fibrosis-4 index, LSMs: Liver stiffness measurement score, AT: After treatment (within 1 month after treatment), BT: Before treatment, LTFU: Long-term followup, SD: Standard deviation

to F1 fibrosis. One of the 5 patients who had F3 fibrosis before treatment (20%) remained at F3, none of them progressed to F4 fibrosis, and 4 patients (80%) regressed to F0-1 fibrosis. Four of the 6 patients (66.66%) who had F2 fibrosis before treatment regressed to F0-1 fibrosis, and 2 patients (33.34%) remained at F2. While 1 of the 4 F0-1 patients (25%) progressed to F3 fibrosis, 3 of the 4 F0-1 patients (75%) remained at F0-1. A decrease was detected in liver stiffness scores in the posttreatment and LTFU analyses compared with LSM values at baseline measurements. The regression detected

Table 5. Rates of regression in values at the beginning and end of treatment and comparison of these regression rates

		AST	ALT	APRI	FIB-4	LSMs	PLT	Bilirubin
INR	r	0.02	0.01	0.07	0.16	-0.25	-0.08	0.19
	p	0.918	0.948	0.701	0.409	0.212	0.686	0.341
AST	r	-	0.91	0.85	0.58	0.37	0.01	-0.01
	p	-	<0.001*	<0.001*	0.002*	0.059	0.936	0.963
ALT	r	-	-	0.73	0.38	0.36	0.01	-0.16
	p	-	-	<0.001*	0.050	0.067	0.956	0.411
APRI	r	-	-	-	0.86	0.28	-0.18	0.12
	p	-	-	-	<0.001*	0.152	0.379	0.559
FIB-4	r	-	-	-	-	0.09	-0.40	0.23
	p	-	-	-	-	0.967	0.040*	0.45
LSMs	r	-	-	-	-	-	0.33	0.10
	p	-	-	-	-	-	0.092	0.603
PLT	r	-	-	-	-	-	-	-0.13
	p	-	-	-	-	-		0.950

*There is a significant difference between groups

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, INR: International normalized ratio, AT: After treatment (within 1 month after treatment), BT: Before treatment, LTFU: Longterm follow-up, LSMs: Liver stiffness measurement score, PLT: Platelet count, FIB-4: Fibrosis-4

Table 6. Rates of regression in values at the beginning of treatment and during the long-term follow-up treatment and comparison of these regression rates

		AST	ALT	APRI	FIB-4	LSMs	PLT	Bilirubin
INR	r	0.23	0.17	0.41	0.31	0.25	0.22	0.30
	p	0.246	0.389	0.034*	0.121	0.210	0.281	0.128
AST	r	-	0.93	0.80	0.66	0.23	-0.04	0.06
	p	-	<0.001*	<0.001*	<0.001*	0.258	0.838	0.742
ALT	r	-	-	0.72	0.51	0.26	-0.03	-0.02
	p	-	-	<0.001*	0.007*	0.186	0.870	0.742
APRI	r	-	-	-	0.87	0.37	-0.27	-0.02
	p	-	-	-	<0.001*	0.062	0.870	0.912
FIB-4	r	-	-	-	-	0.29	-0.47	0.30
	p	-	-	-	-	0.147	0.014*	0.124
LSMs	r	-	-	-	-	-	-0.21	0.01
	p	-	-	-	-	-	0.294	0.985
PLT	r	-	-	-	-	-	-	-0.05
	p	-	-	-	-	-		0.783

*There is a significant difference between groups

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, INR: International normalized ratio, AT: After treatment (within 1 month after treatment), BT: Before treatment, LTFU: Long-term followup, LSMs: Liver stiffness measurement score, PLT: Platelet count, FIB-4: Fibrosis-4

in LSM values in the pre-treatment and LTFU analyses was statistically significant (p=0.005); although there was a regression in the post-treatment and LTFU analyses, the difference was not statistically significant (p=0.107) (Table 3). There was no statistically significant difference in terms of LSM values in the pre-treatment, post-treatment, and LTFU analyses between the groups (p=0.946) (Table 4). There was no significant correlation between the regressions in LSM values and the changes in other parameters in the baseline, post-treatment, and LTFU analyses (Tables 5-7).

Discussion

DAA, which have been approved in 2014 have provided a SVR up to 99%; therefore, liver-related mortality and morbidity rates have started to decrease[13]. Determination of hepatic fibrosis is important for the choice of treatment protocol and for the monitoring of disease prognosis. Current guidelines suggest that the combination of direct biochemical markers and transient fibroelastography is the most effective approach to evaluate the severity of liver disease and fibrosis[8,9]. High SVR rates after treatment with DAA have led to questions such as; does hepatic fibrosis may recur or not, how long it may take to observe regression, if any. There is a limited number of studies conducted for DAA therapies. Huang et al.[14] recorded LSMs, APRI, and FIB-4 scores as well as liver biopsy reports before and after the treatment in 40 patients treated with DAA medications in 2019. Patients were followed for 1 year. In the patient group with the regression of the fibrosis, significantly lower LSM, APRI, and FIB-4 values were detected before the treatment. Comparison of values obtained before and after treatment with DAA revealed a significant decrease in LSM and APRI levels between the fibrotic and non-fibrotic groups; however, the difference was not statistically significant. In our study, we detected higher fibrosis scores at the beginning of the study in the sofosbuvir group; however, there was no statistically significant difference between the liver stiffness regression rates of the treatment groups after a 28-month follow-up. Treatment may cause better regression in patients with advanced fibrosis. Giannini et al.[15] followed 52 cirrhotic patients with grade 3 fibrosis for a median period of 60 weeks. The follow-up revealed regression in liver stiffness level, and both APRI (p<0.0001) and FIB-4 scores (p=0.025) decreased progressively, while an increase was detected in platelet levels (p=0.003). All these outcomes revealed that efficient therapy with DAA may regress portal hypertension[15]. Similarly, the initial and long-term LSM values regressed in our study and the regression were statistically significant (p=0.001, p=0.005 respectively). Similar to the study by Giannini et al.[15], the regression in LSMs reflected the improvements in clinical progress during the LTFU. Furthermore, we observed that the improvement

Table 7. Rates of regression in values at the end of treatment and during the long-term follow-up treatment and comparison of these regression rates

		AST	ALT	APRI	FIB-4	LSMs	PLT	Bilirubin
INR	r	0.12	0.06	0.19	0.01	0.09	0.03	-0.261
	p	0.532	0.754	0.337	0.988	0.650	0.858	0.197
AST	r	-	0.77	0.73	0.41	0.29	-0.02	-0.16
	p	-	<0.001*	<0.001*	<0.037*	0.138	0.917	0.434
ALT	r	-	-	0.64	-0.01	0.15	0.20	-0.14
	p	-	-	<0.001*	0.990	0.441	0.328	0.483
APRI	r	-	-	-	0.32	0.30	-0.08	-0.38
	p	-	-	-	0.108	0.135	0.666	0.053
FIB-4	r	-	-	-	-	0.32	-0.75	-0.11
	p	-	-	-	-	0.105	<0.001*	0.575
LSMs	r	-	-	-	-	-	-0.17	-0.05
	p	-	-	-	-	-	0.395	0.786
PLT	r	-	-	-	-	-	-	-0.04
	p	-	-	-	-	-	-	0.836

*There is a significant difference between groups

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, INR: International normalized ratio, AT: After treatment (within 1 month after treatment), LSMs: Liver stiffness measurement score, PLT: Platelet count, FIB-4: Fibrosis-4

in LSM values achieved during the 60 weeks were maintained for 28 months on average. A previous study conducted in 80 patients diagnosed with CHC who received DAA combination therapies including sofosbuvir reported significant regression in LSMs at 6 months after the treatment ($p<0.001$). In the same study, a significant decrease was found in APRI, FIB-4, AST, ALT, bilirubin, INR and hemoglobin values ($p<0.001$) at 6 months after the treatment, and the improvement in liver stiffness, APRI ($p=0.002$), AST ($p=0.04$), ALT ($p=0.04$), bilirubin ($p=0.03$) values were shown to be positively correlated[16]. In this study, in the Sofosbuvir and Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir treatment group, significant regression was detected in ALT, AST, and INR levels compared with the baseline, and a significant improvement and increase were detected in platelet levels after the 28-week follow-up period. It was concluded based on these results that an efficient and permanent viral response in DAA therapy may result in permanent and continuous improvement in all laboratory parameters. In the study of Tufan et al.[17] in 40 patients treated with DAA, the LSM regressed during the early period after the treatment. A significant regression was detected in the APRI scores at the end of the treatment ($p<0.001$). The significant decrease in LSM in the early posttreatment period indicated that DAA medications efficiently inhibit the persistent inflammation cascade and may provide a rapid improvement in the liver stiffness rate[17]. Similar to other studies, a significant decrease was found in APRI and FIB-4 scores both in the early period after treatment ($p<0.01$) and in the LTFU after treatment in our study ($p<0.01$). Furthermore, a positive correlation between the regression in APRI scores and AST as well as ALT ($p<0.001$), a positive correlation between FIB-4 and AST as well as APRI ($p<0.001$), and a negative correlation was detected between FIB-4 and platelet counts ($p<0.05$) in the post-treatment and LTFU analyses. Improvement in platelet and INR values may indicate a decreased level of liver fibrosis and an increased functional capacity of the liver.

Singh et al.[18] presented a meta-analysis of 24 studies including follow-up periods of 6 to 12 months after permanent viral response, and detected a higher level of regression in liver stiffness between the baseline and post-treatment values. In our study, the most significant recovery in fibrosis was detected in the early period and continued up to 28 months during the follow-up visits.

Study Limitations

LTFU of the patients is difficult due to low patient compliance in our country conditions. Therefore, the number of patients compliing and participating in our study has been limited to 26 for 28 months. The small number of patients in the study is a limitation of this study.

Conclusion

Higher SVR obtained after treatment with DAA reflect on clinical presentation and the improvement of the liver tissue. Such structural recovery of the liver may be detected through liver biopsy and non-invasive methods including APRI, FIB-4 and stiffness measurements may also be used to obtain accurate results. This study has the longest follow-up period of patients monitored through LSMs by non-invasive methods after treatment for hepatitis C. Considering the results we have obtained, we may conclude that hepatic recovery is a dynamic process and continues in the long-term after the treatment.

Ethics

Ethics Committee Approval: Ethics Committee of Clinical and Laboratory Research of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital with the number of 2020/8-25 (date: 08.07.2020).

Informed Consent: Verbal and written consent were obtained from patients participating in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.D.H., Concept: G.D.H., Design: G.D.H., Data Collection or Processing: G.D.H., A.G.T., Analysis or Interpretation: G.D.H., A.G.T., Literature Search: G.D.H., A.G.T.,Writing: G.D.H.

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