Research Article

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An Evaluation of Chronic Hepatitis C Patients' Responses to Direct-Acting Antivirals According to Transient Elastography and Serum Biomarkers

Kronik Hepatit C Hastalarının Direkt Etkili Antivirallere Yanıtlarının Transient Elastografi ve Serum Biyomarkerleri Eşliğinde Değerlendirilmesi

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ABSTRACT

Objectives: In this study, it was evaluated the changes in liver stiffness measurements measured by AST to Platelet Ratio index (APRI), Fibrosis 4 index (FIB-4), Age Platelet index (API), AST-ALT ratio (AAR) and transient elastography (TE) among the non-invasive fibrosis scores in chronic hepatitis C (CHC) patients treated with direct-acting agents (DAA) and the effect of treatment.

Materials and Methods: Ombitasvir-paritaprevir-ritonavir-dasabuvir ± ribavirin (RBV) or sofosbuvir ± ledipasvir (SOF ± LDV) ± RBV was given to the patients. Fibrosis scores were calculated with the biochemical data of the patients before the treatment, at the 4th week of the treatment, at the end of treatment and at the sustained virological response 12 (SVR12). Liver stiffness measurements were recorded before treatment with TE and in SVR12. Post-treatment SVR12 responses were evaluated.

Results: SVR12 was achieved in 97.9% of 95 patients included in the study. Significant regression was found in APRI and FIB-4 scores, which are among the 4 serum fibrosis markers calculated in all patients (p<0.001, p<0.001). Liver stiffness was measured using TE in 75 patients. It was determined that the liver stiffness measurement (9.3±6.5 kPa) in SVR12 significantly decreased compared to the baseline (11.6±7.8 kPa) (p<0.001).

Conclusion: DAA provides improvement in fibrosis scores and persistent viral response in patients. In our study, in which fibrosis was evaluated non-invasive methods, it was observed that there was a significant improvement in liver fibrosis with APRI, FIB-4 and TE measurements.

Keywords: Hepatitis C, direct-acting antivirals, liver fibrosis, transient elastography, APRI, FIB-4

ÖZ

Amaç: Bu çalışmada direkt etkili ajanlarla (DEA) tedavi edilen kronik hepatit C hastalarında non-invaziv fibrozis skorlarından AST to Platelet Ratio index (APRİ), Fibrosis 4 indeks (FIB-4), Age Platelet index (APİ), AST-ALT ratio (AAR) ve transient elastografi (TE) ile ölçülen karaciğer sertlik ölçümlerindeki değişiklikleri ve tedavinin etkisini değerlendirmek amaçlanmıştır.

Gereç ve Yöntemler: Hastalara ombitasvir-paritaprevir-ritonavir-dasabuvir ± ribavirin (RBV) veya sofosbuvir ± ledipasvir (SOF ± LDV) ± RBV verildi. Hastaların tedavi öncesinde, tedavinin 4. haftasında, tedavi sonunda ve kalıcı virolojk yanıt 12'de (KVY12) bakılan biyokimyasal verileri ile fibrozis skorları hesaplandı. TE ile tedavi öncesi ve KVY12'de karaciğer sertlik ölçümleri kaydedildi. Tedavi sonrası KVY12 yanıtları değerlendirildi.

Bulgular: Çalışmaya alınan 95 hastanın %97,9'unda KVY12 elde edildi. Hastaların tamamında hesaplanan 4 serum fibrozis belirteçlerinden APRİ ve FIB-4 skorunda anlamlı gerileme, saptandı (p<0,001, p<0,001). Yetmiş beş hastada TE ile karaciğer sertliği ölçümü yapıldı. KVY12'deki karaciğer sertlik ölçümünün (9,3±6,5 kPa), başlangıca göre (11,6±7,8 kPa) belirgin oranda gerilediği belirlendi (p<0,001).

Sonuç: DEA, hastalarda kalıcı viral yanıtın yanı sıra fibrozis skorlarında iyileşme de sağlamaktadır. Fibrozisin non-invaziv yöntemlerle değerlendirildiği çalışmamızda APRİ, FIB-4 ve TE ölçümleri ile karaciğer fibrozisinde belirgin iyileşme olduğu görülmüştür.

Anahtar Kelimeler: Hepatit C, direkt etkili antiviraller, karaciğer fibrozisi, transient elastografi, APRİ, FIB-4

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Introduction

Hepatitis C virus (HCV) infection is one of the most important causes of chronic liver diseases worldwide. HCV is a slowly progressive disease, characterized by progressive and persistent hepatic inflammation. Cirrhosis develops within 20 years in 20-30% of chronic hepatitis C (CHC) patients, and 1-4% of patients developing cirrhosis progress to hepatocellular carcinoma (HCC) every year (1).

The main objective of treatment in CHC is to achieve sustained virological response (SVR) and cure. Cure permits eradication of the infection. Due to the success of treatment with direct-acting agents (DAA), all patients with CHC are potential candidates for antiviral therapy. Early treatment is very important in terms of preventing potential complications of CHC. The treatment decision in CHC patients is generally based on serum HCV-RNA, genotype, alanine aminotransferase (ALT) levels, and the degree of necroinflammation at liver biopsy and the stage of liver fibrosis (2,3). Biopsy, regarded as the gold standard in the evaluation of fibrosis in liver diseases, entails a number of difficulties, including being invasive, the risk of being unable to obtain sufficient sample, the possibility of different histopathological features occurring in different regions, variations in interpretation among pathologists, and low acceptance rates among patients. This has led to the development of non-biopsy, non-invasive methods in the evaluation of fibrosis (4). The current guidelines describe a combination of direct biochemical markers [AST to Platelet Ratio index (APRI), Fibrosis 4 index (FIB-4), AST-ALT ratio (AAR), Age Platelet index; (API) etc.] and transient elastografi (TE) as the most effective approach in assessing the severity of chronic liver disease and fibrosis (2,5).

Recent studies have reported that fibrosis can regress, although these have particularly involved patients receiving interferon (IFN) therapy (6). The number of studies examining changes occurring in non-invasive fibrosis values and liver stiffness measurements in patients treated with DAA is limited. The purpose of the present study was therefore to investigate responses to treatment in patients receiving DAA therapy, and also the effect of treatment on fibrosis, using non-invasive fibrosis scores and TE.

Materials and Methods

Approval for this study was granted by the Karadeniz Technical University Scientific Research Ethical Committee, Turkey (approval number: 2019/042). The research was performed retrospectively among patients under follow-up with diagnoses of CHC and receiving DAA. Patients completing DAA therapy and attending regular follow-ups for at least 12 weeks were included in the study. Patients' demographic characteristics, viral loads, HCV genotypes, stage of disease and DAA used in treatment were recorded.

HCV-RNA, aspartate aminotransferase (AST), ALT, alpha fetoprotein (AFP), alkaline phosphatase (ALP), gamma-glutamil transferase (GGT), total bilirubin, albumin, protein, blood urea nitrogen, creatinine, international normalized ratio (INR), prothrombin time, hemoglobin (HB), white blood cell (WBC), and platelet (PLT) levels were assessed at the beginning of treatment, four weeks after commencing treatment, at the end of treatment (EOT), and 12 weeks after the EOT. Responses were evaluated based on the levels of these parameters during follow-up.

Fibrosis scores (APRI, FIB-4, AAR and API) were calculated from routinely requested biochemical tests before treatment, four weeks after commencing treatment, at the EOT, and 12 weeks after the EOT (7,8). The courses of the changes in these were recorded and evaluated at the four different time points. In addition, degrees of fibrosis in TE liver stiffness measurement results were recorded before and 12 weeks after the EOT. F_{0-1}<7.1 kPa was regarded as no/mild fibrosis, F_2=7.1-9.4 kPa as moderate fibrosis, F_3=9.5-12.4 kPa as severe fibrosis, and F_4≥12.5 kPa as cirrhosis.

Undetectable HCV-RNA measured using the quantitative polymerase chain reaction (PCR) test on the 12th week after completion of treatment was regarded as SVR (2). HCV-RNA was determined with real-ime PCR, using HCV Quantitative test version 2.0 (Roche Molecular Systems, USA) on a COBAS TaqMan platform.

Statistical Analysis

Statistical analysis was performed on IBM SPSS version 23.0 software. Descriptive statistics were expressed as mean, standard deviation, minimum, and maximum values for numerical variables. The chi-square test was applied in the comparison of qualitative data. Normality of distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Since the data were not normally distributed, the Friedman test was applied to compare measurement variables between two dependent groups, while the Wilcoxon test was used to compare more than two dependent groups. The post-hoc Bonferroni test was applied to identify the source of any significant difference emerging between the groups. Since the data were not normally distributed, Spearman's correlation analysis was applied in the evaluation of relationships between liver stiffness values obtained using TE and other biochemical values and fibrosis scores. Statistical alpha significance was set at $p<0.05$.

Results

Ninety-five patients receiving DAA with a diagnosis of CHC at the Karadeniz Technical University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Turkey, were included in the study. Forty-seven (49.5%) patients were men and 48 (50.5%) women, with a mean age of 62.6±10.5 years. The most common genotype was genotype 1 at 96.8% (n=92), followed by genotype 3 at 2.1% (n=2), and genotype 4 at 1.1% (n=1). In addition, 91.3% of the genotype I patients were genotype 1b. Analysis showed that 47.4% (n=45) of the patients were treatment-naïve and 52.6% (n=50) were treatment-experienced, while 80% (n=76) were non-cirrhotic and 20% (n=19) were cirrhotic. Decompensated cirrhosis was present in one cirrhotic patient (Table 1).

A ombitasvir-paritaprevir-ritonavir-dasabuvir (PrOD) regimen was applied to 57.9% (n=55) of patients, and an sofosbuvir (SOF) regimen to 42.1% (n=40). While 56.8% (n=54) of patients were started on PrOD, 1.1% (n=1) were started on PrOD + ribavirin (RBV), 25.3% (n=24) on SOF/ledipasvir (LDV), 14.7% (n=14) on SOF/LDV + RBV, and 2.1% (n=2) on SOF + RBV. In terms of

responses to treatment, SVR was achieved in 97.9% (n=93) of all patients. HCV-RNA elevation was again observed 12 weeks after completion of treatment in two patients, despite response having been achieved. Serum HCV-RNA, ALT, AST, AFP, ALP, GGT, total bilirubin, protein, albumin, WBC, PLT, and INR values investigated before treatment, at the 4th week of treatment, at the EOT, and SVR12 are shown in Table 2. Changes observed with treatment were statistically significant.

The courses during treatment of the APRI, FIB-4, AAR, and API scores calculated before commencement of treatment are shown in Table 3. APRI, FIB-4, and API decreased on the 4th week of treatment and at the EOT, while an increase was observed in AAR. The decrease in APRI persisted in SVR12 after treatment, while an increase was observed in FIB-4, AAR and API at SVR12 compared to at the EOT. The changes in the APRI, FIB-4 and AAR fibrosis scores were statistically significant (p<0.001, p<0.001, p<0.001).

Post-hoc Bonferroni analysis was applied in order to determine the timing of statistically significant differences in fibrosis scores. Accordingly, the decreases between pretreatment APRI and FIB-4 scores and those on the other weeks were found to be statistically significant. The increases in AAR scores on the other weeks compared to pretreatment values were also statistically significant (Table 4).

TE was used to measure liver stiffness before treatment and at SVR12 in 75 patients. Mean liver stiffness values were 11.6±7.8 kPa and 9.3±6.5 kPa, respectively, and the decrease at SVR12 was statistically significant (p<0.001) (Figure 1).

F_{0-1} fibrosis was determined in 34.7% (n=26) before treatment, F_2 in 17.3% (n=13), F_3 in 13.3% (n=10), and F_4 in 34.7% (n=26). 50% (n=13) of the pretreatment 26 F_4 patients remained at F_4, while 19.2% (n=5) improved to F_3, 11.5% (n=3) to F_2, and 19.2% (n=5) to F_{0-1}. 20% (n=2) of the 10 pretreatment F_3 increased to F_4, 10% (n=1) remained at F_3, 50% (n=5) improved to F_2, and 20% (n=2) improved to F_{0-1}. In addition, 92.3% (n=12) of the 13 pretreatment F_2 patients improved to F_{0-1}, and 7.7% (n=1) increased to F_3. Moreover, 34.7% (n=26) of patients were F_{0-1} before treatment and 76.9% (n=20) remained as F_{0-1}, while 15.4% (n=4) progressed to F_2, and 7.7% (n=2) to F_3. In addition, the 34.7% (n=26) of patients who were F_{0-1} before treatment increased to 52% (n=39) at SVR12, while the incidence of F_3 decreased from 13.3% (n=10) to 12%, F_2 from 17.3% (n=13) to 16% (n=12), and F_4 from 34.7% (n=26) to 20% (n=15) (Figure 2).

The relationships between liver stiffness measurements obtained with TE and biochemical parameters and non-invasive fibrosis scores were also investigated. Negative correlation was determined between liver stiffness values and AAR and PLT

Table 1. Demographic characteristics of the patients

Characteristics	**n (%)**
Mean age ± standard deviation	62.6±10.5
Gender	
Women	48 (50.5%)
Men	47 (49.5%)
HCV genotype	
Genotype 1*	92 (96.8%)
Genotype 3	2 (2.1%)
Genotype 4	1 (1.1%)
Treatment-naive	45 (47.4%)
Treatment-experienced	50 (52.6%)
Non-cirrhotic	76 (80%)
Cirrhotic	19 (20%)

*Genotype 1: 1b, 1a and non-subtyped, HCV: Hepatitis C virus

Table 2. Laboratory values of the patients before treatment, at the 4th week of treatment, at the EOT and SVR12

Laboratory	**Before treatment [mean ± SD (min.-max.)]**	**4th week [mean ± SD (min.-max.)]**	**EOT [mean ± SD (min.-max.)]**	**SVR12 [mean ± SD (min.-max.)]**	**p**
HCV-RNA	1,725,952,6±6,534,968,8 (336-60,050,000)	9.9±45.9 (0-413)	0	340,105,3±2,945,926,3 (0-28.500,000)	**<0.001**
ALT	67.7±64.7 (10-377)	22.6±20.7 (3-124)	18.5±14.8 (3-77)	17.6±15.3 (4-132)	**<0.001**
AST	67.5±57.5 (13-363)	28.8±16.3 (7-113)	26.4±13.8 (6-93)	25.6±11.2 (7-80)	**<0.001**
AFP	11.5±22.7 (1.2-149.2)	7.3±13.6 (0.9-121.9)	5.4±12.1 (0.7-116.4)	4.8±8.5 (0.8-78.1)	**<0.001**
ALP	94.3±38.7 (41-227)	93.5±37.1 (44-254)	99.0±38.5 (44-254)	90.0±38.7 (32-282)	**0.005**
GGT	73.5±76.3 (10-524)	37.2±29.0 (10-236)	27.2±19.9 (8-161)	26.2±15.9 (9-136)	**<0.001**
Total bilirubin	0.9±0.5 (0.1-3.1)	1.0±0.5 (0.2-2.9)	0.9±0.5 (0.3-3.6)	0.9±0.4 (0.3-2.5)	**0.001**
Protein	7.5±0.7 (2.5-8.6)	7.5±0.4 (6.1-8.4)	7.5±0.6 (4.2-8.5)	7.6±0.6 (4-9)	**0.027**
Albumin	4.0±0.4 (2.8-4.8)	4.0±0.4 (2.9-4.7)	4.2±0.5 (2.9-7.4)	4.3±0.4 (3.0-6.2)	**<0.001**
INR	1.0±0.2 (1-2)	1.1±0.2 (0.9-1.5)	1.1±0.2 (0.8-2.2)	1.1±0.2 (1-2)	**0.015**
WBC	6,559,2±2,491,5 (2,590-15,800)	6,917,0±2,298,2 (2,500-16,890)	6.714.3±2.116.7 (2,300-13,800)	6.619.5±2.042.8 (2,900-12,830)	0.160
PLT	196,736,8±77,971,5 (57,000-432,000)	202,389,5±74,709,1 (58,000-366,000)	205,494,7±75,127,7 (57,000-465,000)	202,410.5±74,632,5 (63,000-495,000)	0.192

EOT: End of treatment, SVR12: Sustained virologic response 12, SD: Standard deviation, min.: Minimum, max.: Maximum, HCV: Hepatitis C virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, AFP: Alpha fetoprotein, ALP: Alkaline phosphatase, GGT: Gamma-glutamil transferase, INR: International normalized ratio, WBC: White blood cell, PLT: Platelet

values, while positive correlation was determined with APRI, ALT, AST, AFP, total bilirubin, ALP, GGT, and INR (Table 5).

Discussion

HCV is one of the main causes of chronic liver disease worldwide (1). Liver damage in patients can range from minimal histological changes to advanced fibrosis. If the infection is not treated, it can result in cirrhosis, HCC, and death.

The objective in the treatment of CHC is cure. Current DAA therapies exhibit high effectiveness, a high-barrier viral resistance effect, and a low side-effect profile (9). Several clinical studies have shown that SVR exceeding 90% has been achieved in patients treated with DAA (10,11).

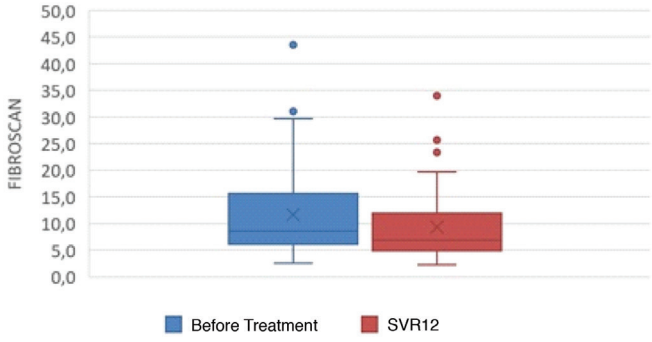

Figure 1. Changes in fibroscan values with treatment

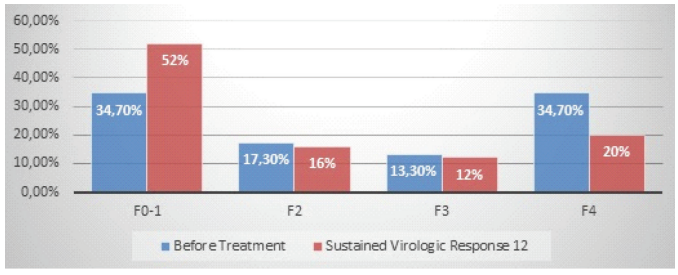

Figure 2. Fibrosis stage before treatment and at SVR12 according to fibroscan value

Before treatment, the degree of necrosis and inflammation in the liver must be graded, fibrosis must be scored, other hepatic pathologies must be excluded, and the treatment options and duration must be determined (12). Several serological and biochemical marker methods have been developed for the non-invasive evaluation of liver fibrosis (4,13). APRI and FIB-4, indirect biochemical markers frequently employed among the non-invasive methods are accepted by current guidelines for the determination of the degree of fibrosis (2). One study investigating the specificity and sensitivity of serum biomarkers and liver stiffness in determining fibrosis in patients diagnosed with CHC compared the effectiveness of biopsy APRI, FIB-4 and TE in 81 patients, and reported that all three were effective in determining liver fibrosis (14). Köksal et al. (15) showed that the non-invasive markers APRI, FIB-4, API and the Forns index exhibited good performances in determining liver fibrosis, and that that the use of at least two tests together would further enhance their diagnostic value.

Another study evaluating changes in liver fibrosis using TE, APRI and FIB-4 in CHC patients treated with DAA achieved an SVR12 rate of 92.7%. Significant decreases in TE, APRI and FIB-4 were observed in all patients 12 weeks after treatment, and particularly in those with more advanced fibrosis (p<0.001) (16).

Comparison of pre-treatment measurements and those at the 4th week of treatment, at the EOT, and at SVR12 revealed a significant decreased in pretreatment APRI scores and those at the other weeks (p<0.001), and that this decrease persisted after the 4th week of treatment. The significant decrease in APRI scores, calculated using AST and PLT values, particularly in the first four weeks, may be associated with a rapid decrease in AST values. A significant decrease was observed between pretreatment FIB-4 scores and the other weeks (p<0.001), although an insignificant increase was determined between the EOT and SVR12 (p=1.000). The significant increase between pretreatment AAR scores and

Table 3. Fibrosis scores before treatment, at the 4th week, at the EOT and SVR12

Fibrosis scores	Before treatment (mean ± SD)	4th week (mean ± SD)	EOT (mean ± SD)	SVR12 (mean ± SD)	p
APRI	1.4±1.9	0.5±0.5	0.5±0.4	0.4±0.3	**<0.001**
FIB-4	3.4±3.0	2.5±1.9	2.3±1.5	2.4±1.5	**<0.001**
AAR	1.1±0.6	1.6±0.7	1.7±0.7	1.8±0.7	**<0.001**
API	5.8±2.2	5.7±2.2	5.6±2.1	5.8±2.1	0.229

EOT: End of treatment, SVR12: Sustained virologic response 12, SD: Standard deviation, APRI: AST to Platelet Ratio Index, FIB-4: Fibrosis 4 Index, AAR: AST-ALT ratio, API: Age Platelet Index,

Table 4. The results of posthoc bonferroni analysis performed for the patients' fibrosis scores before treatment, at the 4th week of treatment, at the EOT and SVR12

Fibrosis scores	Posthoc Bonferroni analysis					
	BT-4th week	BT-EOT	BT-SVR12	4th week-EOT	4th week-SVR12	EOT-SVR12
APRI	**<0.001**	**<0.001**	**<0.001**	0.694	1.000	1.000
FIB-4	**<0.001**	**<0.001**	**<0.001**	1.000	1.000	1.000
AAR	**<0.001**	**<0.001**	**<0.001**	0.864	1.000	1.000

EOT: End of treatment, SVR12: Sustained virologic response 12, BT: Before treatment, APRI: AST to Platelet Ratio Index, FIB-4: Fibrosis 4 Index, AAR: AST-ALT ratio

the other weeks (p<0.001) was evaluated as incompatible with APRI and FIB-4 scores. No significant change was observed in API scores between any time points (p=0.229).

The number of studies evaluating early changes in fibrosis scores with DAA therapies is limited. Hsu et al. (17) evaluated the rapid decrease in non-invasive fibrosis scores in patients diagnosed with CHC receiving DAA therapy. APRI and FIB-4 scores were calculated on the second and 4th weeks of treatment, at the EOT, and at SVR12. Scores decreased rapidly and statistically significantly from the second week until SVR12. Since healing in fibrosis is a long-term process, the authors attributed the early decrease in non-invasive scores at the second week of treatment to the rapid decrease in AST and ALT values and to improvement in necroinflammation as a result of increased PLT values, rather than to improvement of fibrosis (17). Similarly, Elsharkawy et al. (18) reported a significant decrease in ALT levels and APRI scores in the 4th week among patients receiving an SOF-based regimen, and suggested that the early decrease in APRI values reflected a diminution of necroinflammation, rather than regression of fibrosis (18). Similarly in the present study, significant regression was observed in APRI and FIB-4 at the 4th week (p<0.001, p<0.001), which we attributed to a rapid decrease in AST and ALT values. Although regression in APRI and FIB-4 non-invasive fibrosis scores is a finding supporting histological improvement, further prospective studies comparing scores with liver biopsy are now needed in order to confirm this.

Several studies have investigated SVR rates among different DAA therapies, although research into these therapies' effects on histological improvement is insufficient. Carvalho et al. (19) evaluated regression in fibrosis developing after one year in patients receiving IFN-based therapy and DAA therapy using TE, APRI and FIB-4. SVR data were accessed for 105 patients receiving DAA and 73 receiving IFN-based therapy, and statistically significant decreased were observed in APRI, FIB-4 and TE values. Fibrosis regression was more significant in the DAA group, independently of patient characteristics, and this was associated only with the therapeutic regimen (19). Another study evaluated changes in fibrosis between groups receiving IFN-based and DAA therapies among 204 patients diagnosed with CHC. TE, APRI, and FIB-4 and biochemical parameters were investigated before treatments and 12 weeks after the EOT. No significant difference was observed between treatment-naive and treatment-experienced patients in all treatment groups, while score changes were significant in both groups (20). In our study, significant regression was observed in APRI and FIB-2 scores before treatment and at SVR12 in patients receiving SOF and PrOD regimens, together with insignificant regression in API scores. Significant decreases were observed in APRI and FIB-4 scores irrespective of whether patients were treatment-naive or experienced, or cirrhotic or non-cirrhotic, while AAR scores increased significantly, and no change was determined in API scores.

Table 5. Comparison of the liver stiffness measurement value measured by TE with other parameters

Liver stiffness	R	p
APRI	0.301	**0.009**
FIB-4	0.172	0.140
AAR	-0.302	**0.008**
API	0.117	0.316
ALT	0.345	**0.002**
AST	0.458	**<0.001**
AFP	0.533	**<0.001**
Total bilirubin	0.329	**0.004**
ALP	0.322	**0.005**
GGT	0.485	**<0.001**
INR	0.511	**<0.001**
WBC	-0.145	0.215
PLT	-0.434	**<0.001**

APRI: AST to Platelet Ratio index, FIB-4: Fibrosis 4 index, AAR: AST-ALT ratio, API: Age Platelet index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, AFP: Alpha fetoprotein, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, INR: International normalized ratio, WBC: White blood cell, PLT: Platelet

Examination of the previous literature shows that long-term follow-up has most frequently involved patients receiving pegylated (PEG)-IFN + RBV therapy, and since the length of use of DAA agents is still short, long-term follow-ups have not been performed. In a prospective study from France, patients with and without PEG-IFN + RBV therapy were followed-up for three years. Changes in liver fibrosis were evaluated using non-invasive methods. Liver stiffness measurements for fibrosis performed with TE before treatment, at the EOT, and six months after completion of treatment for liver fibrosis in the treatment group were compared in the treatment group, while initial values and values at the end of one and two years were compared in the non-treatment group. Significant regression was observed in liver stiffness values in the treatment group between baseline and the EOT (p<0.001). EOT measurements in the treatment group differed significantly from first-year measurements in the non-treatment group (p<0.001) (21).

In their study of 392 patients receiving DAA therapy, Bachofner et al. (22) reported significant improvement, with a regression rate of 32.4%, in TE values after treatment compared to baseline (p<0.001). Regressions in APRI and FIB-4 scores were also significant (p<0.001). Liver stiffness values measured before treatment and at SVR12 in our study were 11.6±7.8 kPa and 9.3±6.5 kPa, respectively. This improvement in liver stiffness was statistically significant (p<0.001).

Tada et al. (23) reported that the improvement in liver fibrosis persisted from the end of DAA therapy until the 24th week in CHC patients achieving SVR. Pons et al. (24) investigated early and long-term liver and spleen stiffness following treatment with DAA and reported that improvement in liver stiffness commenced from the 4th week of treatment (p=0.002), and that the greatest regression was observed in the first four weeks. In addition, improvement persisted throughout treatment, significant improvement was also observed at EOT measurements (p=0.014), persisting until the 48th week post-treatment (p=0.003) (24). These two studies showed that significant improvement in liver stiffness persisted for 48 weeks. The patients in the present study were followed-up for 12 weeks after treatment. In terms of grades based on TE measurement,

the proportion of F_{0-1} patients rose from 34.7% to 52% at SVR12, while the proportion of F_4 patients decreased from 34.7% to 20%. Since the healing process is a continuing one, longer follow-ups are required for a more accurate evaluation. We think that fibrosis regression rates in patients with higher degrees of diseases will be greater at long-term follow-up.

A study from Japan evaluated liver stiffness measurements obtained using TE before treatment and at SVR24 in patients diagnosed with CHC and using DAA. Significant regression was observed at SVR24 in ALT, AST, total bilirubin, INR, HGB, APRI, FIB-4, and liver stiffness, and positive correlation was determined between this improvement in liver stiffness and ALT (p=0.04), AST (p=0.04), total bilirubin (p=0.03), and APRI (p=0.002) (25). In our study, the improvement in liver stiffness was positively correlated with APRI (p=0.009), ALT (p=0.002), AST (p<0.001), AFP (p<0.001), total bilirubin (p=0.004), ALP (p=0.005), GGT (p<0.001) and INR (p<0.001), and negatively correlated with AAR (p=0.008) and PLT (p<0.001). We think that the positive correlation between improvement in liver stiffness and APRI, ALT, and AST is associated with improvement in necroinflammation with treatment, while the positive correlation with INR and negative correlation with PLT are associated with improvement in fibrosis and regulation of hepatic synthesis functions.

Study Limitations

There were limitations to the present study. First, the study was done retrospectively. Second, the number of patients is small. Third, noninvasive scores were not confirmed by biopsy.

Conclusion

DAA therapy was effective in all the patients in this study, and successful SVR was achieved. The study findings showed that cure can be achieved in CHC with treatment, and that early regression in fibrosis scores occurs after treatment. This study also shows that the use of non-invasive fibrosis markers is a simple, effective, and practical method for monitoring fibrosis.

Ethics

Ethics Committee Approval: Approval for this study was granted by the Karadeniz Technical University Scientific Research Ethical Committee, Turkey (approval number: 2019/042).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.N.A., İ.K., Concept: İ.K., Design: İ.K., Data Collection or Processing: N.N.A., Analysis or Interpretation: N.N.A., Literature Search: N.N.A., Writing: N.N.A.

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