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ORIGINAL ARTICLE

The changing non-invasive fibrosis index value in patients with hepatitis C treated with direct-acting antiviral agents

Direkt etkili antiviral ajanlarla tedavi olan hepatit C hastalarında non-invaziv fibrozis indeks değerlerinin değişimi

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Background and Aims: About 400 000 patients with hepatitis C virus die from cirrhosis-related complications and hepatocellular carcinoma every year. Direct-acting antivirals provide a sustained virologic response in more than 90% of patients with hepatitis C virus infection. We aimed to evaluate the alteration of the non-invasive fibrosis index in patients with hepatitis C virus who were treated with direct-acting antivirals. **Materials and Method:** Patients with hepatitis C virus who received a complete course of direct-acting antivirals were analyzed. FIB-4 and APRI were calculated for each patient. **Results:** Of the 88 patients, 46 (52%) were males, and 21 (23.8%) were cirrhotics. The mean age was 58 years. The significant decrease was showed in the non-invasive scores compared from the baseline to the end of treatment. There was a statistically significant drop in mean FIB-4 and APRI scores from baseline to post sustained virologic response ($p < 0.001$). In the long-term follow-up, it was observed to continue low FIB-4 and APRI at 15 months post sustained virologic response. Mean follow up-time was 27.8 ± 24.3 months in our study, and just one patient was diagnosed with hepatocellular cancer after direct-acting antivirals treatment during follow-up. **Conclusion:** An early decline in FIB-4 and APRI scores can be related to a decrease in liver enzymes. Nonetheless, maintaining a low level of non-invasive markers has been linked to a reduction in necroinflammation.

Key words: Direct-acting anti-viral agents, hepatitis C virus, non-invasive fibrosis index

Giriş ve Amaç: Her yıl yaklaşık 400 000 hepatit C virüs hastası siroza bağlı komplikasyonlardan ve hepatosellüler karsinomadan ölmektedir. Doğrudan etkili antiviraller, hepatit C virüs enfeksiyonu olan hastaların %90'ından fazlasında sürekli bir virolojik yanıt sağlar. Bu çalışmada doğrudan etkili antivirallerle tedavi edilen hepatit C virüslü hastalarda non-invaziv fibrozis indeksindeki değişikliği değerlendirmeyi amaçladık. **Gereç ve Yöntem:** Doğrudan etkili antiviral teadavisi alan hepatit C virüslü hastalar analiz edildi. Her hasta için FIB-4 ve APRI hesaplandı. **Bulgular:** Toplam 88 hastanın 46'sı (%52) erkek, 21'i (%23.8) sirotikti. Ortalama yaş 58 yıl idi. Başlangıçtan tedavi bitimine kadar non-invaziv skorlarda anlamlı düşüş gösterildi ($p < 0.001$). Başlangıçtan sürekli bir virolojik yanıt sonrasına kadar ortalama FIB-4 ve APRI skorlarında istatistiksel olarak anlamlı bir düşüş vardı ($p < 0.001$). Uzun süreli takipte, sürekli bir virolojik yanıt sonrası 15 ayda düşük FIB-4 ve APRI'nin devam ettiği gözlendi. Çalışmamızda ortalama takip süresi 27.8 ± 24.3 ay olup, takipte doğrudan etkili antiviral tedavisi sonrası sadece bir hastaya hepatosellüler kanser tanısı konuldu. **Sonuç:** FIB-4 ve APRI skorlarındaki erken düşüş, karaciğer enzimlerindeki azalma ile ilişkili olabilir. Bununla birlikte, takiplerde düşük düzeyde invaziv olmayan skorların devam etmesi, nekroinflamasyonda bir azalma ile ilişkilendirilmiştir.

Anahtar kelimeler: Direkt etkili anti-viral ajanlar, hepatit C virüsü, non-invasiv fibrozis skorları

INTRODUCTION

It is accepted that 58 million people are infected with hepatitis C virus (HCV), and the prevalence of hepatitis C infection is estimated at 1% worldwide (1). The risk of chronic liver disease is at 75-85% of patients with HCV infection; the risk of developing cirrhosis is at 5-25% of chronic liver patients with-

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in 20 years, and hepatocellular carcinoma (HCC) is determined in 3% of cirrhotic patients per year (2).

The gold standard for specifying fibrosis and hepatic inflammation is liver biopsy. On the other hand, liver biopsy is invasive, costly, and carries some serious risks, including bleeding, pneumothorax, and death (3). For the reasons stated, cost-effective, applicable, and non-invasive methods are required (4). The most frequently used tests are aspartate aminotransferase (AST) platelet ratio (APRI) and the fibrosis index based on four factors (FIB-4). FIB-4 with some cut-off values excludes advanced fibrosis (< 1.45) or predicts advanced liver fibrosis (> 3.25). The APRI cut-off value is less than 0.5 for cirrhosis exclusion and higher than 1.5 for advanced fibrosis (≥ F2) estimation (5).

Direct-acting antivirals (DAA's) provide a sustained virologic response (SVR) in more than 90% of patients with HCV infection (6). Various studies indicate SVR is related to the regression of liver cirrhosis and fibrosis. Accordingly to European Association For the Study of Liver (EASL) guideline, it is currently not advised to routinely use non-invasive scores, liver stiffness measurement (LSM) by transient elastography (TE), and other elastography techniques to detect fibrosis regression in HCV patients after SVR (7).

The present study investigated the effect of DAAs on the non-invasive index values of patients with chronic hepatitis C (CHC) at baseline, week 4, end of treatment (EOT), 12 weeks post-EOT and 18 months post-EOT.

MATERIALS and METHOD

Patients with treatment-experienced and treatment-naive HCV who received a complete course of DAA therapy from 2012 to 2017 were enrolled in this retrospective analysis. Inclusion criteria were as follows: age ≥ 18 years, presence of the serum anti-HCV antibody for > 6 months and detectable HCV RNA, and completion of DAA therapy.

Exclusion criteria were as follows: presence of liver disease caused by other etiologies, decompensated liver disease, or cancer.

The patients included in the study; age at diagnosis, gender, routine laboratory tests performed before and during follow-up of DAAs, and pre-treatment liver biopsy results were collected retrospectively from the hospital data management system. The Ishak Modified Hepatitis Activity Index staging system was used for staging of fibrosis in liver needle biopsy histopathology reports of the patients.

FIB-4, which is used in the non-invasive evaluation of fibrosis; according to alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet, and age according to the formula "[age (years) × AST (U/L)] / (platelet (109/L) × ALT (U/L)", APRI score is based on Wai's formula "(AST/upper limit of normal was calculated using 40 IU/L)/platelet count (platelet × 109 /L) × 100" (7,8).

Ethics

This study was conducted in accordance with the Declaration of Helsinki. The Ankara City Hospital Clinical Research Ethics Committee granted approval for this study (number: E2-22-1942, 06/08/2022).

Statistical Analysis

The statistical analysis was performed using IBM SPSS statistics version 25 (IBM corp.). Kolmogorov-Smirnov normality tests were used to evaluate the distribution of variables and an independent sample t-test was used for comparison of two group means. A chi-square test was used to assess the relationships between the nominal variables. Data were presented as means ± standard deviation or number and percentage according to their type and distribution. Differences were considered significant at $p < 0.05$.

RESULTS

Of the 88 patients, 46 (52%) were males, 21 (23.8%) were cirrhotics. The mean age was 58.8 (min-max:18 - 84) years (Table 1). A total of 38 patients (43.2%) were treatment-experienced. The most of patients were HCV genotype 1b (94.3%). The patients were treated with Ombitasvir/Paritoprevir/Ritonavir+Dasabuvir (52%), Ledipasvir/Sofosbuvir (23%), Ledipasvir/Sofosbuvir+Ribavirin (23%). A total of 8 patients were treated with DAAs after liver transplantation. The rate of SVR was 100%.

Table 1 Features of patient demographics and baseline characteristics

Patients (n = 88)	n (%) or Median (IQR)
Age (years)	58.8 (18 - 84)
Sex, M/F (% male)	46/42 (52.2)
Treatment (Naive), n (%)	50 (38)
AST (U/L)	55.7 (18 - 247)
ALT (U/L)	56 (15 - 222)
Total bilirubin (mg/dL)	0.84 (0.33 - 2.2)
Hemoglobin (g/dL)	14 (8.8 - 17)
Platelet count (×10^9/L)	177 (39 - 360)
FIB-4 (IQR) (initial value)	3.06 (0.34 - 9.1)
APRI (initial value)	1.01 (0.32 - 6.4)
Liver cirrhosis, n (%)	21 (23.8)
Liver biopsy (initial), (n: 44)	
F1	15 (34.9)
F2	26 (59.0)
F3	2 (4.5)
F4	1 (2.2)
HCV genotype, n (%)	
1a	2 (2.3)
1b	83 (94.3)
3	2 (2.3)
4	1 (1.1)
SVR, n (%)	88 (100)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FIB 4: Fibrosis 4 score; IQR: Interquartile range; APRI: Aspartate aminotransferase to platelet ratio index; HCV: Hepatitis C virus; SVR: Sustained virologic response.

Figure 1 shows the median values for FIB-4 and APRI at baseline, week 4, EOT, 12 weeks post-EOT and 18 months post-EOT. There was a statistically significant drop in mean FIB-4 and APRI scores from baseline to EOT ($p < 0.001$). In the long-term follow-up, it was observed to continue low FIB-4 and APRI at 15 months post SVR.

The significant decrease observed in all parameters at the end of the treatment remains stable with continued follow-up (Table 2). Sixty five percentage of the patients with baseline FIB-4 score 3.25 were found to have a FIB-4 score < 3.25 at the end of follow-up.

Mean follow up-time was 27.8 ± 24.3 months in our study, and just one patient was diagnosed with hepatocellular cancer after DAA's treatment during follow-up. The patient's liver biopsy was just F4 fibrosis in the study. This patient's APRI and FIB-4 values weren't decreased at follow-up Before treatment with DAA's, two patients were diagnosed with HCC. Both these patients were treated with local ablative treatment (TACE), and there was no recurrence.

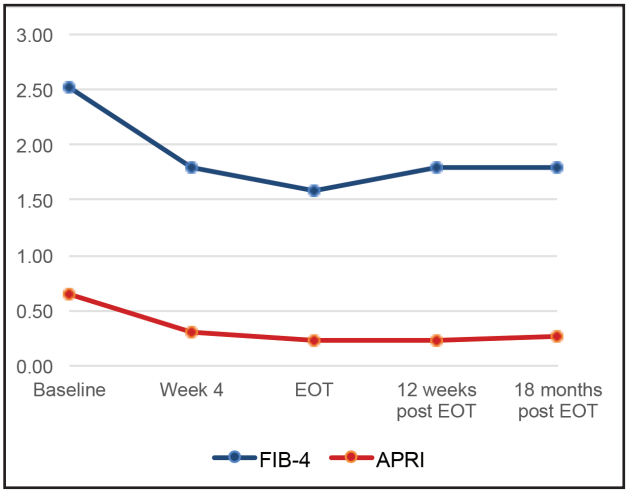

Figure 1 Follow-up mean APRI and FIB-4 scores.

EOT: End of the treatment; FIB 4: Fibrosis 4 score; APRI: Aspartate aminotransferase to platelet ratio index

Table 2 Follow-up AST, ALT, platelets, FIB-4, and APRI for patients

	Baseline vs. EOT			EOT vs. 18 Months Post-Eot		
Variable Median (IQR)	Baseline	EOT	P	EOT	18 Months Post-EOT	P
AST (IU/L)	44.5 (31 - 70)	19 (15 - 24)	<0.001	19 (15 - 24)	21 (17-25)	.147
ALT (IU/L)	46.5 (30 - 71)	14 (11 - 18)	<0.001	14 (11 - 18)	14 (12 - 21)	.237
PLT ($\times 10^9$/L)	174 (130 - 230)	189 (137 - 247)	<0.001	189 (137 - 247)	197 (129 - 246)	.516
FIB-4	2.52 (1.6 - 4)	1.58 (0.99 - 2.8)	<0.001	1.58 (0.99 - 2.8)	1.79 (1.2 - 2.7)	.998
APRI	0.65 (0.4 - 1.2)	0.23 (0.17 - 0.41)	<0.001	0.23 (0.17 - 0.41)	0.26 (0.20 - 0.39)	.714

EOT: End of the treatment; IQR: Interquartile range; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PLT: Platelet; FIB-4: Fibrosis-4 score; APRI: Aspartate aminotransferase to platelet ratio index.

DISCUSSION

The risk of chronic liver disease is unavoidable in patients with HCV infection. The risk of fibrosis increases especially after long-term exposure. Also fibrosis increases the risk of HCC and HCC is determined in 3% of cirrhotic patients per year (2). Chronic HCV infection is held to account for liver fibrosis and activation of the immune system, which induces the proliferation of myofibroblasts and produces extracellular matrix proteins (4).

This study was that the values of APRI and FIB-4 decreased significantly between baseline and EOT evaluation, but there was no difference in the two scores between EOT and 12 months post-EOT. This drop could be due to the typical transaminase readings acquired after starting DAA medication. Our study showed that the early decrease in level of APRI and FIB-4 remained during long-term follow-up after DAA therapy. Similar result showed that DAA treatment of HCV results provided in rapid regression of fibrosis markers FIB-4 and APRI (10). Also, continuousness in decreasing FIB-4 and APRI has been shown in a study that included 251 patients (164 cirrhotic and 83 non-cirrhotic) until 12 months after DAAs (11). There are studies in which AST/ALT ratio and FIB-4 are correlated with treatment response and used as a predictor for SVR estimation (12).

Patients with HCV who achieved SVR while receiving DAA therapy should be closely monitored in the years ahead, as liver cirrhosis and HCC may develop despite viral eradication. Increasing fibrosis is associated with higher liver decompensation and HCC risk. In our study, HCC occurred in one patient during follow-up after treatment with DAAs. Moreover, only F4 fibrosis was present in the patient who developed HCC. Recent research has shown that after treatment with DAAs, the rate of HCC occurrence increases. In the first study, Rinaldi et al. declared the first report an unexpected occurrence rate of HCC (%3.7) (13). Cardoso et al. reported that 7.4% of 54 HCV patients treated with sofosbuvir and ledipasvir for 24 weeks were diagnosed with HCC following a median follow-up of 12.0 months (IQR 9.4–12.5 months) from viral eradication. Although no causative effect for any investigated baseline component in HCC development was revealed, the authors believed that immune system dysregulation could play a role (14). Ioanou et al. stated that 62 354 patients who started antiviral treatment (including 35 871 (58%) interferon (IFN)-only regimens, 4 535 (7.2%) DAA + IFN regimens, and 21 948 (35%) DAA-only regimens) were followed for an average of 6.1 years (15). When compared to IFN treatment, DAA

treatment has not linked to an increased incidence of HCC. Seven hundred ninety three patients with HCV-associated HCC have assessed in a multicenter North American cohort study (16), with 38.3 percent receiving DAAs therapy and 61.7 percent going untreated. HCC recurred in 42.1% of treated individuals and 58.9% of untreated patients. DAAs medication has not linked to an increased risk of overall or early HCC recurrence, according to the authors. Some studies showed that the risk of overall or early HCC recurrence increased after treatment, but these studies did not have a large enough scale population or control group.

The most important limitation of our study, we need large scale population and control grup, especially for determining of HCC risk. Non-invasive imaging approaches (transient/US/MRI elastography etc.) could not be used to combine to evaluate patients' fibrosis. Unfortunately, non-invasive imaging methods could not be performed due to the retrospective study design in our study.

In conclusion, significant changes are observed in fibrosis scores in the short and long term with DAA treatment. It prevents the development of chronic liver or cirrhosis in patients, but it should be kept in mind that HCC may develop in these patients, even if SVR is taken with treatment, and they should be followed closely.

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Ethics: *This study was approved by the Ankara City Hospital Ethics Committee on June 8, 2022, number E2-22-1942.*

Conflict of Interest: *The authors have no conflict of interest to declare.*

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