Real-Life Data on Sofosbuvir/Ledipasvir in Patients with Chronic Viral Hepatitis C Genotype 1b: A Single-Center Experience

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ABSTRACT

Background: *The course of hepatitis C disease has changed with the use of direct-acting antiviral drugs in the treatment of the disease. The aim of this study was to evaluate the real-life efficacy and safety of the sofosbuvir/ledipasvir drug regimen in the treatment of patients with genotype 1b.*

Methods: *Treatment-naive or -experienced 49 genotypes 1b patients treated with sofosbuvir/ledipasvir participated in the study. Laboratory and hepatitis C virus RNA values were evaluated at baseline, week 12, and week 24 of treatment (36th week for those who received 24 weeks of treatment).*

Results: *The sustained virologic response rate was 100% in patients who completed treatment. At the end of the study, there was a significant decrease in alanine transaminase, aspartate transaminase, gamma-glutamyl transferase, and alpha-fetoprotein levels (P = .000014, P = .000581, P = .000012, and P = .000821), respectively. Renal function tests (creatinine, estimated glomerular filtration rate) worsened (P = .003 and P = .007, respectively). Hepatocellular carcinoma (HCC) was developed in 2 patients during post-treatment follow-up. In Kaplan–Meier analysis, the probability of not developing HCC was 86.5% at 26 months.*

Conclusion: *The sofosbuvir/ledipasvir combination is effective in treating genotype 1b chronic hepatitis C with high sustained virologic response rates. Because there are few drug interactions, it may be a suitable option for patients taking multiple medications or who are transplant recipients. Renal function should be monitored closely during and after treatment, as there is a risk of worsening renal function after treatment.*

Keywords: *Chronic hepatitis C, genotype 1b, renal functions, sofosbuvir-ledipasvir*

INTRODUCTION

It is estimated that more than 71 million people worldwide are infected with chronic hepatitis C virus (HCV). This makes it one of the most important causes of chronic liver disease.[1] Acute HCV infections are largely asymptomatic and generally not life-threatening. Approximately 30% of infected individuals recover without the need for treatment. Chronic HCV infection develops in the remaining 70% of patients.[2]

Hepatitis C virus is a major cause of hepatocellular cancer and is associated with fibrosis/cirrhosis.[3] Although HCV mainly affects the liver, many extrahepatic manifestations are also observed. It is estimated that approximately 74% of patients present with at least 1 extrahepatic symptom.[4]

The use of direct-acting antivirals (DAA), which specifically target viral-encoded enzymes critical to the HCV replication cycle, was introduced in 2014 and has transformed the management of HCV infection by demonstrating a high sustained virologic response (SVR) (greater than 95% for main genotypes) with better tolerability and shorter cure times compared to interferon/ribavirin-based regimen.[5-7]

A treatment regimen combining sofosbuvir (SOF), a nucleotide analog of the NS5B polymerase, and ledipasvir (LED), the NS5A inhibitor, was approved by the US Food and Drug Administration for patients infected with HCV genotype 1a or 1b, in October 2014. The duration of treatment (12-24 weeks) and treatment regimen (addition of ribavirin to treatment) vary depending on whether the patient has received prior treatment and which HCV subtype (1a or 1b) the patient has.[8-9] In the ION and LONESTAR trials, SVR rates (SVR12) of patients treated with the SOFT/LEAD regimen reported approximately 95%[10-11] and 100%,[12-13] respectively, after 12 weeks of treatment.

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In our study, we aimed to evaluate the efficacy and safety of the SOF/LED combination (DAA) in the treatment of chronic HCV infection in patients with genotype 1b using real-world data.

MATERIALS AND METHODS

Study Design

Patients with HCV genotype 1b who were admitted to Gastroenterology Polyclinic of Karadeniz Technical University Medical School Farabi Hospital were selected for the study. Patients over 18 years of age, male or female, treatment-naive or -experienced, with or without cirrhosis, and treated with SOF/LED ± ribavirin were included in this study and were analyzed retrospectively (Figure 1).

Data from all patients were kept confidential with anonymized codes and used only for the current study. Before the start of the study, approval was obtained from the Ethics Committee of the Faculty of Medicine, Karadeniz Technical University, with approval number 24237859-450. Informed consent was not obtained from the patients as the study was retrospective. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Individual treatment regimens were determined by the hepatology committee of our hospital according to current guidelines and the recommendations of the national consensus report at baseline. All patients had received either 12- or 24-week treatment according to ribavirin usage status. Ribavirin dosing was determined according to the patients' body weight.

The comorbid diseases of patients were recorded, and other medications of all patients were queried on the website https://www.hep-druginteractions.org/checker and reviewed for possible interactions between SOF and LED.

Main Points

- *Treatment of hepatitis C virus (HCV) infection with new oral direct-acting agents such as sofosbuvir+ledipasvir (SOF+LED) is effective and safe.*
- *Fixed-dose combination of SOF/LED is an effective and safe alternative for HCV genotypes 1 and 4.*
- *Patients with alpha-fetoprotein <30 mL/min/1.73 m^2 must not use SOF+LED.*
- *After SOF+LED treatment patients must be followed for renal functions.*
- *HCC occurrence after curative HCV treatment is still a debate.*

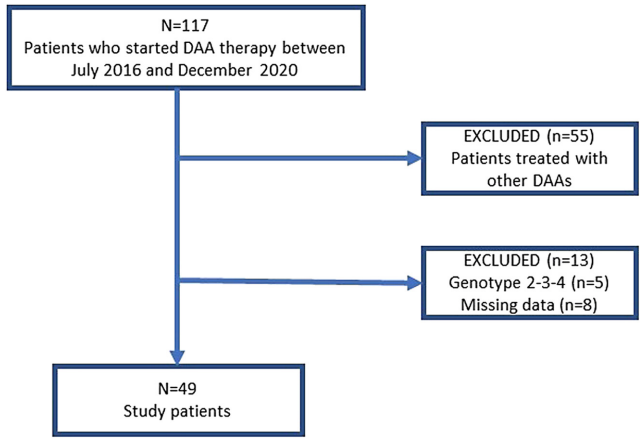

Figure 1. Flowchart of the patients included in the study.

Patients were routinely followed up during antiviral therapy at weeks 4 and 12 and at 24 weeks if there was a 24-week treatment phase. In addition, follow-up visits were scheduled at week 48 after treatment initiation.

Quantitative HCV PCR was performed using commercially available kits (COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v. 2.0, Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. The lower limit of linear detection for HCV RNA is 10 IU/mL and the upper limit is 1 × 109 IU/mL.

In all patients, HCV RNA, glucose, albumin, liver function tests (aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and bilirubin), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), sodium (Na), potassium (K), calcium (Ca), phosphorus (P), alpha-fetoprotein (AFP), international normalized ratio (INR), uric acid, C-reactive protein (CRP), and complete blood count were evaluated at each visit (Table 1).

The SVR was defined as undetectable HCV RNA, ≥12 weeks after completion of therapy.[14]

Statistical Analysis

The Statistical Package for Social Sciences version 22.0 software (IBM Corp.; Armonk, NY, USA) was used to analyze the data. In the descriptive statistics of the evaluation results, numbers and percentages are given

Table 1. Laboratory Values at the Beginning of Treatment

Variable		Variable	
HCV RNA (IU/mL), median (IQR)	216 500 (962 425)	LDH (U/L), mean ± SD	240.72 ± 55.69
Glucose (mg/dL), median (IQR)	108.5 (43)	Na (mEq/L), mean ± SD	137.53 ± 3.79
Albumin (g/L), mean ± SD	3.47 ± 0.65	K (mEq/L), mean ± SD	4.3 ± 0.48
BUN (mg/dL), mean ± SD	16.62 ± 3.81	Ca (mg/dL), mean ± SD	8.83 ± 0.61
Creatinine (mg/dL), mean ± SD	0.69 ± 0.16	P (mg/dL), mean ± SD	3.29 ± 0.58
eGFR (mL/min/1.73 m^2), mean ± SD	93.46 ± 14.04	CRP (mg/L), median (IQR)	0.15 (0.66)
Uric acid (mg/dL), mean ± SD	5.41 ± 1.46	AFP (μg/L), median (IQR)	7.72 (24.5)
ALT (U/L), median (IQR)	49.5 (54)	INR, mean ± SD	1.24 ± 0.23
AST (U/L), median (IQR)	78 (71)	Hgb (g/dL), mean ± SD	12.45 ± 2.17
GGT (U/L), median (IQR)	51 (70)	MCV (fL), mean ± SD	90.36 ± 7.7
ALP (U/L), median (IQR)	107 ± 55	MPV (fL), median (IQR)	10.05 (2.4)
Total bilirubin (mg/dL), median (IQR)	1.17 (0.79)	Platelet (μL), mean ± SD	135787 ± 86231

HCV RNA, hepatitis C ribonucleic acid; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; Na, sodium; K, potassium; Ca, calcium; P, phosphate; CRP, C-reactive protein; AFP, alpha-fetoprotein; INR, international normalized ratio; Hgb, hemoglobin; MCV, mean corpuscular hemoglobin; MPV, mean platelet volume.

for categorical variables, while mean, standard deviation, minimum, and maximum are given for numerical variables. The normal distributions of numerical variables were tested using the Kolmogorov–Smirnov 1-sample test. Comparison of numerical variables between 2 independent groups was evaluated with the Student *t*-test if the normal distribution condition was met and with the Mann–Whitney *U* test if it was not. When comparing numerical variables between 3 or more independent groups, the 1-way analysis of variance test is evaluated when the condition of normal distribution is met, and the Kruskal–Wallis test when it is not. The chi-square test is used to analyze the differences between the ratios of the categorical variables in the independent groups. The statistical significance level (alpha) is accepted as $P < .05$.

RESULTS

The mean age of the patients was 65.83 (±9) years, and the gender distribution was 49% (n = 24) male and 51% (n = 25) female; 42.9% (n = 21) of patients were non-cirrhotic, and 57.1% (n = 28) were cirrhotic; 67.8% (n = 19) of the cirrhotic patients had compensated cirrhosis, and 32.2% (n = 9) had decompensated cirrhosis (Table 2).

The genotype of all patients included in the study was 1b. While 85.7% (n = 42) of patients received only SOF/LED fixed-dose combination treatment, 14.3% (n = 7) received SOF/LED + ribavirin combination treatment. The duration of treatment was 12 weeks in 18.4% (n = 9) of patients and 24 weeks in 81.6% (n = 40). Of 55.1% (n = 27) patients were treatment-naive, and 44,9% were treatment experienced (40.8% (n = 20) pegylated interferon 1b + ribavirin combination, and 4.1% (n = 2) pegylated interferon 1b only). (Table 3). There was no significant difference in the use of SOF/LED ± ribavirin in patients who were treatment-naive or experienced.

The most common comorbidities were hypertension 46.9% (n = 23), diabetes mellitus 34.7% (n = 17), malignancies 18.4% (n = 9), hypothyroidism 10.2% (n = 5), coronary artery disease 10.2% (n = 5), valvular heart disease 8.2% (n = 4), chronic kidney disease 6.1% (n = 3), and congestive heart failure 6.1% (n = 3) (Table 4).

Hepatosteatosis was absent in 73.5% (n = 36) of patients, by USG. And grade 1 and grade 2 hepatosteatosis was found in 12.2% (n = 6), and 4.1% (n = 2) respectively.

Table 2. Demographic Characteristics

Variable	
Age, mean ± SD	65.83 ± 9
Male/female, n (%)	24 (49)/25 (51)
Non-cirrhotic, n (%)	21 (42.9)
Cirrhotic	28 (57.1)
Compensated	19 (67.8)
Decompensated	9 (32.2)

Table 3. Treatment Regimens and Durations

Variable	n (%)
Treatment regimen	42 (85.7)
SOF/LED	7 (14.3)
SOF/LED + Ribavirin	
Treatment duration	9 (18.4)
12 weeks	24 (81.6)
24 weeks	
Treatment experience	27 (55.1)
None	20 (40.8)
Pegylated interferon 1b+Ribavirin	2 (4.1)
Pegylated interferon 1b	

SOF/LED, sofosbuvir/ledipasvir.

In 5 patients, the report of abdominal imaging was not accessible, so no evaluation could be performed.

Regarding the development of Hepatocellular carcinoma (HCC) after antiviral treatment, 28 patients (57.1%) were followed up with abdominal imaging. The median follow-up time was 25.3 (±14.5) months. It was observed that HCC developed in 2 patients (7.1%). One of the patients who developed HCC was noncirrhotic, whereas the other had compensated cirrhosis. While HCC developed after 26 months in the non-cirrhotic patient, it occurred after 10 months in the cirrhotic patient. In the Kaplan–Meier analysis, the probability of cases not having HCC at 26 months was 86.5% (Figure 2).

Table 4. Comorbidities

Systemic disease	n (%)
Hypertension	23 (46.9)
Diabetes mellitus	17 (34.7)
Malignities	9 (18.4)
Hepatocellular carcinoma	4 (44.5)
Renal cell carcinoma	1 (11.1)
Colon cancer	1 (11.1)
Bladder cancer	1 (11.1)
Prostate cancer	1 (11.1)
Lymphoma	1 (11.1)
Hypothyroidism	5 (10.2)
Coronary artery disease	5 (10.2)
Valvular heart disease	4 (8.2)
Chronic kidney disease	3 (6.1)
Chronic heart failure	3 (6.1)
Arrhythmia	2 (4.1)
Asthma	2 (4.1)
Liver transplantation	2 (4.1)
Benign prostatic hyperplasia	2 (4.1)
Cerebrovascular disease	1 (2)
Primary biliary cholangitis	1 (2)
Idiopathic thrombocytopenic purpura	1 (2)

Before the treatment the median HCV RNA value was 216,500 IU/mL (2,540-8,340,000 IU/mL). Hepatitis C virus RNA was negative in 90.3% (n = 28) of 31 patients whose HCV RNA was evaluated after 4 weeks of treatment. Sustained virologic response was achieved in all 49 patients who completed their treatment (100%).

Alanine transaminase, AST, and GGT levels were significantly decreased after antiviral therapy (median ALT 44 U/L before treatment and 18.5 U/L at the end of treatment [P = .000014], median AST 63 U/L before treatment and 30 U/L at end of treatment [P = .000581], and median GGT 38 U/L before treatment and 25.5 U/L at end of treatment [P = .000012]) (Figure 3).

There was a significant increase in creatinine levels after treatment and a significant decrease in eGFR (mean serum creatinine 0.67 mg/dL before treatment versus 0.76 mg/dL at the end of treatment [P = .003]; mean serum eGFR 94.94 mL/min/1.73 m^2 before treatment versus 87.7 mL/min/1.73 m^2 at the end of treatment [P = .007]) (Figure 4). There was no significant difference between the BUN values before and after treatment (P = .1).

A significant decrease in AFP (median value 7.04 µg/L before treatment and 4.92 µg/L after treatment [P = .000 821]) was observed before and after treatment (Figure 5).

There was no statistically significant difference in other laboratory values measured before and after treatment ($P > .05$).

CONCLUSION

The introduction of DAA drugs is a turning point in the treatment of chronic HCV infection. Thanks to DAA therapies, it is now possible to treat patients who previously could not be treated due to interferon intolerance, advanced cirrhosis/decompensation, or concomitant diseases. As a result of their good tolerability and high safety profile, high SVR rates have been achieved and treatment duration shortened.

Interferon-based antiviral therapies had significantly lower SVR rates in practice than in clinical trials.[10,15] Treatment

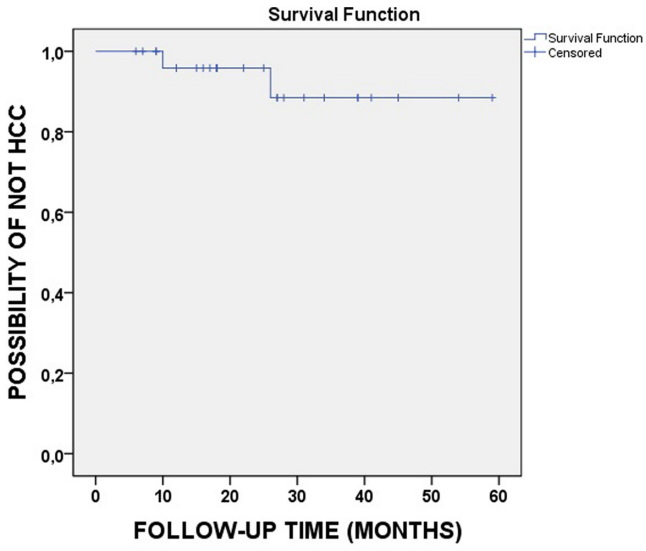

Figure 2. Kaplan–Meier analysis of the probability of not having HCC.

with SOF/LED results in very high SVR rates (99%) in non-cirrhotic patients.[10,11] Also in our study, the success rate was 100% in patients who completed treatment (per-protocol analysis).

Sofosbuvir/Ledipasvir is a once-daily tablet (fixed-dose combination) regimen. This simple regimen may improve patient compliance. In the study conducted by Ioannou et al[16] the rate of patients discontinuing treatment after less than 8 weeks was found to be 6.9% of all patients and 5.2% of patients with cirrhosis. In the same study, the rate of early discontinuation of SOF/LED was significantly lower (between 5.7% and 8.9%, $P < .001$) compared to treatment with paritaprevir/ritonavir/ombitasvir and dasabuvir. Despite not having a serious adverse event profile, only 1 (2%) of the patients excluded from our study voluntarily discontinued treatment at the end of the first month.

Both SOF and LDV have limited interactions with other drugs.[17,18] This is an advantage, especially in patients who have undergone renal or liver transplantation or who are taking multiple medications because of concomitant diseases. Because the average age of our patients was high, they had additional diseases and were taking multiple medications. We had 2 patients who had liver transplantation. In these patients, we achieved 100% SVR without any drug interaction or side effects.

In the study by Huang et al[19] it was shown that inflammation and fibrosis in the liver decreased after the use of DAA. The fact that the levels of ALT, AST and GGT were significantly decreased after treatment in our study ($P = .000014$, $P = .000581$, and $P = .000012$, respectively) supports this result.

Renal excretion of SOF and ribavirin is a possible cause of renal toxicity. In our study, there was a significant increase in creatinine levels ($P = .003$) and decrease in eGFR levels ($P = .007$) at 6 months after treatment. In a study by Butt et al[20] patients receiving SOF/LED therapy who had an eGFR >60 mL/min/1.73 m^2 prior to treatment had a rate of 37.8% patients with a decrease in eGFR of >10 mL/min/1.73 m^2. In our study, the mean serum creatinine and eGFR values before and after treatment were 0.67 mg/dL versus 0.76 mg/dL [$P = .003$] and 94.94 mL/min/1.73 m^2 versus 87.7 mL/min/1.73 m^2 [$P = .007$], respectively), and the mean eGFR decrease was 7.24 mL/min/1.73 m^2 (Figure 4).

Although AFP is a glycoprotein normally produced by the fetal liver and yolk sac during pregnancy, its serum concentration may be elevated in patients with HCC. The risk of HCC has been shown to be increased in patients

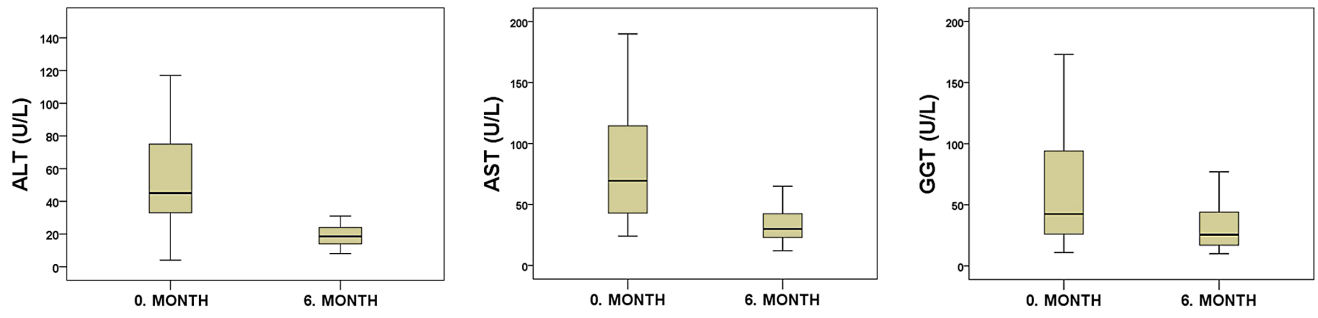

Figure 3. ALT, AST, GGT levels (U/L) before and after treatment. ALT, alanine transaminase; AST, aspartate transaminase, GGT, gamma-glutamyl transferase.

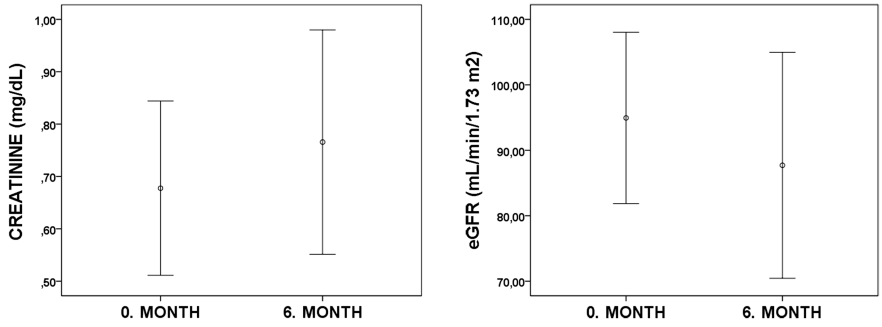

Figure 4. Creatinine (mg/dL) and eGFR (mL/min/1.73 m^2) values before and after treatment. eGFR, estimated glomerular filtration rate.

with chronic liver disease and high AFP levels.[21] In studies performed in patients with chronic liver disease, the sensitivity of AFP to detect HCC was about 60% and the specificity was about 80%.[22] In our study, there was a significant decrease in AFP levels before and after treatment (*P* = .000821).

Studies have shown that a high SVR rate is associated with a lower risk of hepatic decompensation, the need for liver transplantation, and a decrease in liver-related and overall mortality.[23] Although expectations of a significant reduction in the incidence of HCC because of SVR are increasing, the effect of HCC development in patients with cirrhosis and the incidence of HCC recurrence after successful treatment are controversial.[24-26] In a meta-analysis of 26 studies and 11523 patients, DAA treatment was not associated with a higher incidence of HCC in patients with cirrhosis.[27] In the study conducted by Cheung et al.[28] the incidence of HCC at 12 months in cirrhotic patients after DAA treatment was 6.7%, whereas this rate was reported to be 0.9% in cirrhotic/noncirrhotic patients at 18 months by Calleja et al[29] and 7.4% in cirrhotic patients at 12 months by Cardoso et al.[30] In our study, after follow-up with abdominal imaging for an average of 25.3 months after antiviral treatment, it was observed that HCC developed in 2 (7.1%) of 28 patients, 1 of whom was not cirrhotic (26 months later) and the other had compensated cirrhosis (at 10th month) (Figure 2).

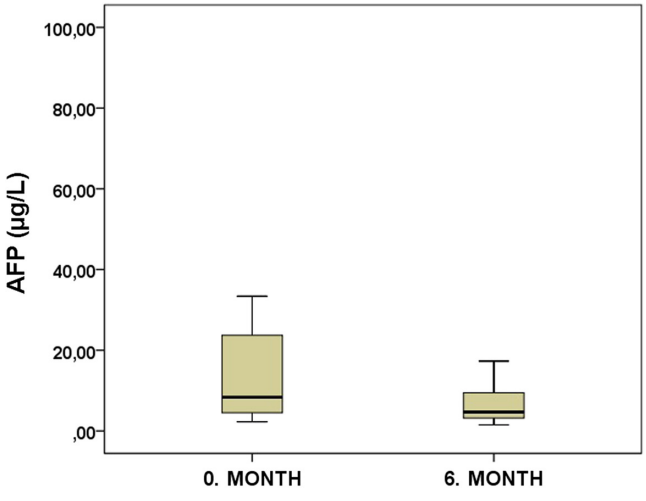

Figure 5. AFP levels (µg/L) before and after treatment. AFP, alpha-fetoprotein.

Our study has some limitations because of its retrospective nature, the number of cases, and the heterogeneous patient population. However, we believe it will contribute to the literature when evaluated with similar studies because it contains real-life data.

In this study, it is supported that the combination of SOF/LED can achieve high SVR rates in a population dominated by the chronic hepatitis C 1b genotype. The fixed-dose combination of SOF/LED with low drug interactions could be a good option because chronic hepatitis C patients are older and most of them have comorbidities and take multiple medications. However, due to the renal excretion of SOF and ribavirin and the possible worsening of renal function, as well as the limitation of use in patients with a GFR <30 mL/min, it has been indicated that it is important to monitor renal function during and after treatment in all patients. Clearly, longer-term follow-up studies are needed to monitor patients for the development of HCC.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Karadeniz Technical University, (Approval No: 24237859-450).

Informed Consent: No informed consent was needed because of the retrospective non-interventional study design.

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