Real-life experience of ledipasvir and sofosbuvir single-tablet regimen among chronic hepatitis C patients in Turkey

Tansu Yamazhan[1], İlker Turan[2], Galip Ersöz[2], Fulya Günşar[2], Hüsnü Pullukçu[1], Nilay Danış[2], Nalan G. Ünal[2], Rukiye Vardar[2], Nevin Oruç[2], Fatih Tekin[2], Meltem Taşbakan[1], Oğuz R. Sipahi[1], Ulus S. Akarca[2]

[1]Department of Infectious Disease, Ege University, İzmir, Turkey
[2]Department of Gastroenterology, Ege University, İzmir, Turkey

Cite this article as: Yamazhan T, Turan İ, Ersöz G, et al. Real-life experience of ledipasvir and sofosbuvir single-tablet regimen among chronic hepatitis C patients in Turkey. Turk J Gastroenterol 2020; 31(3): 239-45.

ABSTRACT

Background/Aims: Ledipasvir (LDV) and sofosbuvir (SOF) as single-tablet regimen (STR) has been approved for treatment of chronic HCV infection (CHC) for treatment-naïve or experienced cirrhotic or non-cirrhotic patients. Our aim was to analyse the effectiveness and safety of 12-24 weeks treatment of LDV/SOF (90mg/400 mg)±ribavirin in a real-life setting in Turkey.

Materials and Methods: Between May-Dec 2016, 104 treatment-naïve or experienced adult patients with CHC and with or without cirrhosis (including decompensated cirrhosis) were included in this observational study. Patients were administered LDV/SOF STR± ribavirin once daily for 12 -24 weeks. SVR12 rates and effects of the baseline characteristics on SVR12 rates were assessed.

Results: Out of 104 enrolled patients (61.5% female, mean age 62.0 years); 60.6% were cirrhotic, 76.0% previously used peg-IFN, 94.2% had GT1. At the end of the treatment, 77.8% (77/99, no data for 21 patients) had undetectable HCV-RNA and 98.9% (94/95) had SVR12. In the baseline characteristics subgroups, the SVR12 rates varied between 94.4% and 100%, and none of the baseline characteristics had a significant effect on the SVR12 rates. During the study, 6 (5.8%) patients died and none of the deaths was suspected to be related to the LDV/SOF. No treatment-emergent adverse event was reported.

Conclusion: In conclusion, LDV/SOF±ribavirin yielded very high SVR12 rates, without any safety or tolerability concern in Turkey. The effectiveness of the LDV/SOF treatment was not affected by the patient demographics or medical characteristics such as fibrosis level, cirrhosis status, previous treatment status, HCV-RNA level or HCV genotype.

Keywords: Ledipasvir, Turkey, sofosbuvir, chronic hepatitis C, effectiveness, safety

INTRODUCTION

The World Health Organization reported that the hepatitis C virus (HCV) infection represents a global public health problem, and its highest prevalence was found in the Eastern Mediterranean region (2.3%) and Europe (1.5%) (1). In Turkey, the prevalence of anti-HCV positivity was reported at 0.95% (2). The pegylated interferon and ribavirin were the only treatment options available for the HCV infection, with a limited sustained virologic response (SVR) rate, until 2011. Since then, the treatment success rate has dramatically improved due to the use of direct-acting antivirals and their combinations (DAAs). In late 2014, the HCV treatment approaches were completely changed by the launch of the second-generation DAAs, and a full recovery from the HCV infection became possible (3)genotype 1 was significantly more aggressive when utilizing the combination of pegylated interferon and ribavirin, as genotype 1-infected patients had the lowest likelihood of achieving cure (40%-50%.

The first approved second-generation DAAs combination was a single-tablet regimen (STR) of ledipasvir (LDV) and sofosbuvir (SOF). LDV and SOF are DAA: SOF is a potent NS5B nucleotide polymerase inhibitor, showing a pan-genotypic activity and a high barrier of resistance, whereas LDV is an HCV NS5A inhibitor with a potent antiviral activity against the HCV genotypes 1, 3, 4, 5, and 6 (3,4)genotype 1 was significantly more aggressive when utilizing the combination of pegylated interferon and ribavirin, as genotype 1-infected patients had the lowest likelihood of achieving cure (40%-50%.

Based on the ION-1 trial (a randomized controlled multicenter Phase III trial), the 12-24 week treatment of LDV/SOF (90 mg/400 mg), with or without ribavirin, provided a 97%-99% SVR in the HCV Genotype 1 treatment-naïve patients (5). A similar efficacy results of 94%-99% SVR with a 12-24 week treatment of LDV/SOF (90 mg/400 mg), with or without ribavirin, among the HCV Genotype 1 treatment-experienced patients were reported in the

Corresponding Author: **Tansu Yamazhan; tansu.yamazhan@ege.edu.tr**
Received: **January 30, 2019** Accepted: **March 29, 2019**

DOI: **10.5152/tjg.2020.19076**

ION-2 trial (randomized controlled multicenter Phase III trial) (6). Relatively a shorter treatment duration (8 weeks) was evaluated in the treatment of the naïve HCV Genotype 1 non-cirrhotic patients (ION-3 randomized controlled multicenter Phase III trial), and 93%-95% SVR were reported. The non-inferiority analysis revealed that the treatments lasting 8 and 12 weeks resulted in a similar SVR (7).

Although the ION-1 and ION-2 trials reported that the use of LDV/SOF (90 mg/400 mg) was effective in the compensated cirrhotic patients, the SOLAR1 and SOLAR2 trials (randomized controlled multicenter Phase II trials) evidently exhibited that the LDV/SOF (90 mg/400 mg), with or without ribavirin, is an effective treatment for the HCV Genotype 1- or HCV Genotype 4-infected patients with an advanced liver disease, including decompensated cirrhosis before or after liver transplantation (8,9)open-label study, we assessed treatment with the NS5A inhibitor ledipasvir, the nucleotide polymerase inhibitor sofosbuvir, and ribavirin in patients infected with HCV genotypes 1 or 4. Cohort A enrolled patients with cirrhosis and moderate or severe hepatic impairment who had not undergone liver transplantation. Cohort B enrolled patients who had undergone liver transplantation: those without cirrhosis; those with cirrhosis and mild, moderate, or severe hepatic impairment; and those with fibrosing cholestatic hepatitis. Patients were assigned randomly (1:1.

The LDV (90 mg) and SOF (400 mg) STR were first approved under the trademark of Harvoni in October 2014 in the United States and then, in February 2015 in Turkey, for the treatment of chronic HCV infection (CHC). Since then, it has been used in the treatment of naïve or experienced cirrhotic or non-cirrhotic patients with CHC. The recommended treatment duration is 12 to 24 weeks, depending on the HCV genotype and concomitant ribavirin treatment (3,4)genotype 1 was significantly more aggressive when utilizing the combination of pegylated interferon and ribavirin, as genotype 1-infected patients had the lowest likelihood of achieving cure (40%-50%. In this study, we aimed to analyze the effectiveness and safety of a LDV/SOF (90 mg/400 mg) treatment lasting between 12 and 24 weeks, with or without ribavirin, in a real-life setting in Turkey.

MATERIALS AND METHODS

Patient selection and treatment

Between May 2016 and December 2016, the treatment-naïve or -experienced adult patients with CHC and with or without cirrhosis (including decompensated cirrhosis) were included in this observational study. Patients received LDV (90 mg) and SOF (400 mg) STR once every day with or without ribavirin (800-1200 mg/day based on patient's weight) at physician's discretion for 12 or 24 weeks. The physicians prescribed the treatment according to the summary of product characteristics, which were approved by the Turkish Ministry of Health.

All procedures followed were in accordance with the ethical standards of the responsible institutional ethics committee and with the latest version of the Helsinki Declaration. Informed consent was obtained from all patients included in the study.

Follow-up and data collection

Due to the observational nature of the study, no intervention to the physicians' practice was defined. However, all the participating physicians were expected to follow the recommendation of guidelines on the chronic HCV-infected patients. The recommendations included the evaluation of the patient at weeks 4, 12, and 24 (treatment end) after the treatment had started and at 12 weeks after the treatment end to evaluate the rate of SVR12. The demographics and medical characteristics, including the HCV genotype (Abbott RealTime HCV Genotype II assay), of patients were recorded at the time of starting the LDV/SOF treatment. The medical status of the patient, the HCV-RNA level (Abbott RealTime HCV assay), death, and adverse events were also recorded during the entire follow-up duration. During the follow-up, laboratory tests, i.e., alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, serum creatinine, and the international normalized ratio values were also recorded, if any available.

Statistical analysis

The primary outcome of this study was SVR12, which was defined as an undetectable HCV-RNA level. The undetectable HCV-RNA level was defined as a laboratory lower limit of quantification of <12 IU/ml. No sample size calculation was performed, as all the eligible patients in the study period were aimed to be enrolled. The main analysis of the population was intent to treat the population. The results were summarized by the descriptive statistics, and the change over time was analyzed by non-parametric tests. The data handling and statistical analysis operations were performed using the Statistical Package for Social Sciences version 21.0 (IBM Corp.; Armonk, NY, USA).

RESULTS

Patient disposition

Of the eligible 111 patients, 104 were able to receive the LDV/SOF treatment and were enrolled in the study. After the enrolment, 2 patients were lost to follow-up, and 2 died. In total, 99 patients completed the treatment. One patient was lost due to follow-up, 3 patients died after the treatment end, and 95 patients underwent an SVR12 evaluation (Figure 1).

Demographics and medical characteristics

Of 104 enrolled patients, 61.5% (64/104) were female, the mean (standard deviation, SD) age of the patients was 62.0 (12.5) years, and all were Caucasian. More than half the patients (60.6%; 63/104) were cirrhotic, whereas 44.4% (28/63) of the cirrhotic patients were decompensated, and none had a history of liver transplantation. Three-quarters of patients (76.0%, 79/104) were previously treated with pegylated interferon-based treatments. The patients used mostly (82.7%, 86/104) LDV/SOF (90 mg/400 mg) alone, while others used LDV/SOF (90 mg/400 mg)+ribavirin. Almost three-quarters of patients (73.1%, 76/104) underwent the treatment for 24 weeks, whereas others had it for 12 weeks. The most common HCV genotype was Genotype 1 (94.2%, 98/104; Genotype1b 63.5%, Genotype 1 unable to detect the subtype 24.0%, and Genotype 1a 6.7%) followed by Genotype 3 (2.9%, 3/104) and Genotype 4 (2.9%, 3/104). Of the patients with the Child-Pugh class data, 35.6% (16/45) had the Child-Pugh Class A, whereas 53.3%

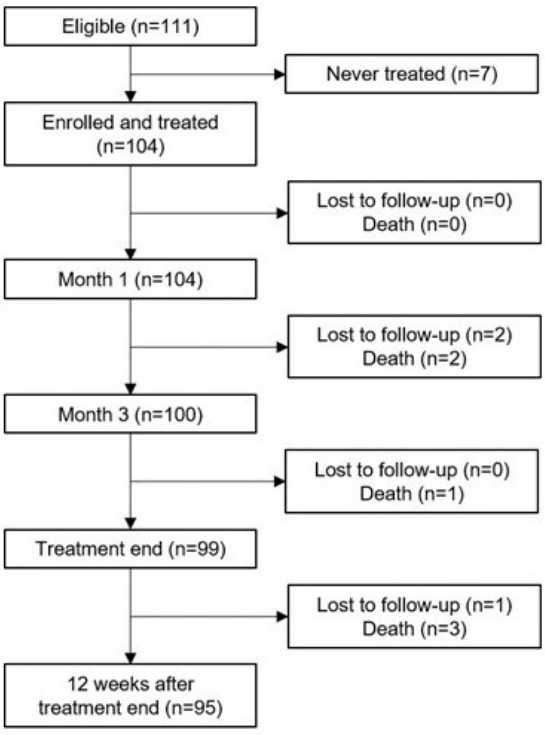


Figure 1. SVR12 evaluation.

Table 1. Demographics and medical characteristics of patients.

	All patients (n=104)
Gender, female; n (%)	64 (61.5%)
Age, years; mean (SD)	62.0 (12.5)
Race, Caucasian n (%)	104 (100%)
Cirrhosis; n (%)	
Non-cirrhotic	41 (39.4%)
Cirrhotic	63 (60.6%)
compensated	35 (55.6%)*
decompensated	28 (44.4%)*
Previous treatment for HCV; n (%)	
Treatment naïve	25 (24.0%)
Treatment experienced	79 (76.0%)
Previous liver transplantation; n (%)	0 (0.0%)
HCV genotype; n (%)	
GT1	98 (94.2%)
GT 1a	7 (6.7%)
GT 1b	66 (63.5%)
GT 1 untypeable	25 (24.0%)
GT 3	3 (2.9%)
GT 4	3 (2.9%)
MELD score before LDV/SOV treatment; median (IQR)	10 (8-14)
Child-Pugh class; n (% in 45)	
A	16 (35.6%)
B	24 (53.3%)
C	5 (11.1%)
Treatment; n (%)	
LDV/SOF (90mg / 400 mg)	86 (82.7%)
LDV/SOF (90mg / 400 mg)+ribavirin.	18 (17.3%)
Treatment duration; n (%)	
12 weeks	26 (25.0%)
24 weeks	76 (73.1%)
No record	2 (1.9%)

IQR: inter-quartile range, LDV: ledipasvir, MELD: model for end stage liver disease, SD: standard deviation, SOF: sofosbuvir.
*percentage of cirrhotic patients.

(24/45) had Class B, and 11.1% (5/45) had class C. The median model for the end-stage liver disease score was 10 (the interquartile range [IQR], 8-14) at the beginning of the LDV/SOF treatment (Table 1).

HCV-RNA

The median HCV-RNA level was 695,531 IU/mL before the LDV/SOF treatment, and it reduced to 0 IU/mL 4 weeks after the initiation of the treatment and stayed as 0 IU/mL during the entire follow-up and until 12 weeks after the treatment end (P<0.001 for all time points vs. baseline) (Supplementary Figure 1).

None of the patients had undetectable HCV-RNA (<12 IU/mL) before being treated by LDV/SOF. At the treatment end, the percentage of patients with undetectable HCV-RNA reached 77.8% (77/99, no data were available for 21 patients), and 98.9% (94/95) had SVR12. The HCV-RNA levels of 2 patients who had undetectable HCV-RNA previously, became detectable (1 at the time of treatment end and the other one 12 weeks after the treatment end) (Table 2, Figure 2).

Among the treatment-experienced patients, 80.8% had undetectable HCV-RNA at the treatment end (remaining patients had no data) and 100% SVR12, whereas among the treatment-naïve patients, 66.7% had undetectable HCV-RNA at the treatment end (6 patients had no data) and 94.4% SVR12. A total of 2 treatment-naïve patients exhibited virologic failure at the treatment end and 12 weeks after the treatment end, respectively (Table 2, Figure 3). In the other baseline characteristics subgroups, the SVR12 rates varied between 94.4% and 100%, and none of the baseline characteristics had

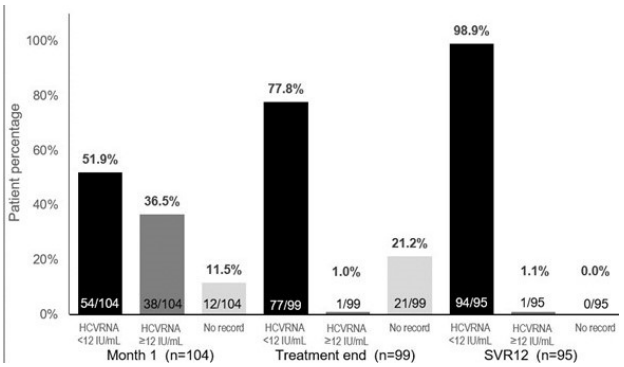


Figure 2. Treatment-end, the percentage of patients with undetectable HCV-RNA.

Table 2. Patient percentage with undetectable HCV-RNA over the time.

% (n)	HCV-RNA <12 IU/mL	HCV-RNA ≥12 IU/mL	No record
All patients			
Baseline (n=104)	0.0% (0)	100% (104)	0.0% (0)
Month 1 (n=104)	51.9% (54)	36.5% (38)	11.5% (12)
Month 3 (n=100)	23.0% (23)	4.0% (4)	7.03% (73)
Treatment-end (n=99)	77.8% (77)	1.0% (1)	21.2% (21)
SVR12 (n=95)	98.9% (94)	1.1% (1)	0.0% (0)
Treatment experienced			
Baseline (n=79)	0.0% (0)	100% (79)	0.0% (0)
Month 1 (n=79)	55.7% (44)	35.4% (28)	8.9% (7)
Month 3 (n=79)	22.8% (18)	3.8% (3)	73.4% (58)
Treatment-end (n=78)	80.8% (63)	0.0% (0)	19.2% (15)
SVR12 (n=77)	100% (77)	0.0% (0)	0.0% (0)
Treatment naïve			
Baseline (n=25)	0.0% (0)	100% (25)	0.0% (0)
Month 1 (n=25)	40.0% (10)	40.0% (10)	20.0% (5)
Month 3 (n=21)	23.8% (5)	4.8% (1)	71.4% (15)
Treatment-end (n=21)	66.7% (14)	4.8% (1)	28.6% (6)
SVR12 (n=18)	94.4% (17)	5.6% (1)	0.0% (0)

SVR12: sustained virologic response at 12 weeks after treatment-end.

a significant effect on the SVR12 rates (for all baseline characteristics subgroups comparisons, P>0.05) (Figure 3).

Safety

During the course of the treatment, 6 (5.8%) patients died: 3 during and 3 after the treatment. None of the deaths was suspected to be related to the LDV/SOF treatment. An adverse event was reported in 2 (1.9%) patients, and the events reported were headache and asthenia. These events were mild in severity and were not suspected to be related to the LDV/SOF treatment.

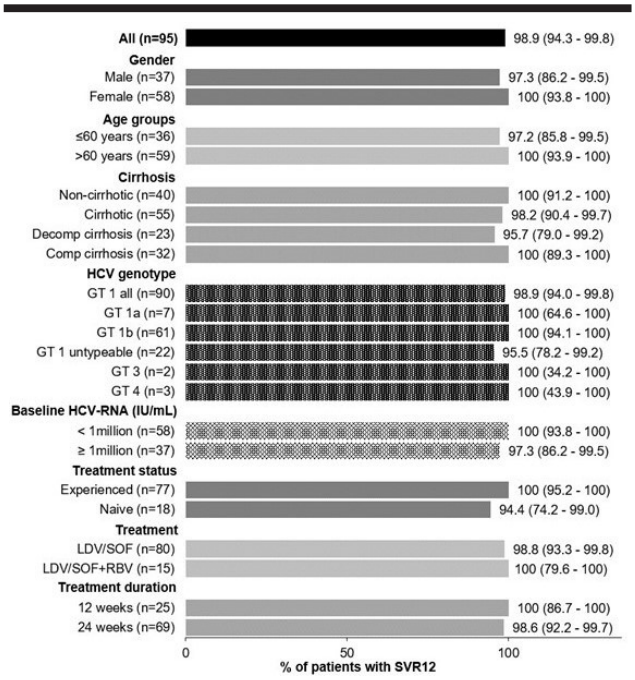


Figure 3. Virologic failure at the treatment-end and 12 weeks after treatment-end.

The median (IQR) ALT level decreased from 43 (29-67) IU/mL before the LDV/SOV treatment to 19 (14-25) IU/mL at the treatment end, whereas the AST level decreased from 50 (31-72) IU/mL to 22 (19-28) IU/mL at the treatment end. No clinically significant change in the total bilirubin, creatinine, international normalized ratio, and serum sodium levels were observed (Table 3).

DISCUSSION

The results of this observational real-world study revealed that the LDV/SOF treatment, with or without ribavirin, yields a higher SVR12 rate (98.9%), and the effectiveness of the treatment is persistent in the patient subgroups including difficulty to treat populations (i.e., treatment-experienced patients or patients with advanced fibrosis-cirrhosis or patients with a baseline HCV-RNA ≥1 million IU/mL). In addition to the high effectiveness, the LDV/SOF treatment was well taken by the CHC patients, and none of the adverse events observed or deaths were suspected to be related to the LDV/SOF treatment.

The LDV/SOF combination has been used for the CHC treatment since late 2014, and the results from the real-world settings in different countries, in addition to the clinical trials, have been published in the last couple of years. In a secondary analysis of a large database for the United States, a total of 4,365 treatment-naïve Genotype 1 CHC patients were treated with LDV/SOF, with or without ribavirin, for 8 to 12 weeks. The SVR12 rates were found to be 91.3% and 92.0% in LDV/SOF only and LDV/SOF with ribavirin, respectively. The authors also reported that being African American and having a FIB-4 score >3.25 were significantly associated with the lower SVR12 rates, whereas age, gender, body mass index, decompensated liver disease, diabetes mellitus, Genotype 1 subtype, and using ribavirin did not have a significant effect on the SVR12 rates (10). In our study, the SVR 12 rates in the treatment-naïve patients and baseline char-

Table 3. Laboratory parameters over the time..

	Before LDV/SOV treatment		Week 4		Treatment-end	
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
ALT (IU/L)	94	43 (29-67)	83	18 (13-27)	47	19 (14-25)
AST (IU/L)	92	50 (31-72)	81	23 (20-33)	47	22 (19-28)
Bilirubin, total (mg/dL)	58	0.93 (0.61-1.6)			24	0.91 (0.58-1.42)
Creatinine (mg/dL)	60	0.72 (0.6-0.97)			21	0.83 (0.62-1.06)
INR	54	1.2 (1.1-1.3)			21	1.1 (1.1-1.2)
Sodium (mmol/L)	42	140 (136-141)			15	137 (136-141)

ALT: alanine transaminase, AST: aspartate transaminase, INR: international normalized ratio, IQR: inter-quartile range.

acteristics groups were slightly higher than those reported by Bascus et al. (10) patients with a decompensated cirrhosis achieved a 95.7% SVR12 rate, whereas those with compensated cirrhosis reached a 100% SVR12 rate, which might signify that the LDV/SOF STR is an efficacious treatment for the CHC regardless of the fibrosis stage of the patients. Higher SVR12 rates, regardless of the fibrosis stage, in our study might be explained by a longer treatment duration, as the reimbursement rules in Turkey require at least 12 weeks of the LDV/SOF treatment, and most of the patients in our study (82.7%) received LDV/SOF for 24 weeks.

In the observational HCV target study, 667 treatment-experienced patients from the United States, Canada, Germany, and Israel were treated with LDV/SOF, with or without ribavirin, for 12 to 24 weeks. The SVR12 rate was 93.8% for all study population and varied between 94.1% and 98.0% for the treatment duration and additional ribavirin usage. In their analysis, Lim et al. (11) reported that having a decompensated cirrhosis or albumin <3.5 g/dL or total bilirubin >1.2 mg/dL were associated with lower SVR12 rates. In our study, we observed that a 100% SVR12 rate in treatment-experienced patients and treatment duration, as well as additional ribavirin usage, seemed to have an unremarkable effect on the effectiveness of the LDV/SOF treatment. Lim et al. (11) concluded that a longer treatment duration and additional ribavirin usage may help increase the suppression rate in patients with decompensated cirrhosis. We have observed that the patients with decompensated cirrhosis had similar SVR12 rates compared to those with or without compensated cirrhosis (95.7% vs 100% vs 100%, respectively), and the effectiveness of LDV/SOF in all the fibrosis stages seemed to be independent of additional ribavirin usage.

In another retrospective cohort study from the United States (Trio Health study), 1,597 treatment-naïve or -experienced patients were applied LDV/SOF, with or without ribavirin, for 12 weeks. The majority of the patients (95.2%) were under the treatment of LDV/SOF without ribavirin, and the SVR12 rate was 94.1%, whereas patients who used LDV/SOF with ribavirin yielded 97.4% of SVR12. In their analysis, Tapper EB et al. (12) found that having cirrhosis or thrombocytopenia were associated with a lower SVR12 rate (12). Our analysis also revealed that adding ribavirin to the LDV/SOF treatment may increase the SVR12 rates. Although we did not observe any increased risk for anemia in our study population, ribavirin is known to be related to severe anemia in patients with a HCV infection; therefore, close monitoring is recommended for ribavirin-related anemia (13). Contrary to the results by Tapper et al. (12) we observed high SVR12 rates, regardless of the cirrhosis status.

Several real-world preliminary data from several centers in Turkey have been published as abstracts recently. These data included treatment-experienced or treatment-naïve patients, cirrhotic or non-cirrhotic patients, geriatric population, and patients with comorbidities. The SVR12 rates after LDV/SOF, with or without ribavirin, for 12 or 24 weeks were reported between 97.0% and 100%; moreover, no special subgroup was reported to be associated with a lower SVR12 rate (14-20).

This study has certain limitations due to the observational nature of the non-randomized design. All the patients with CHC who met the treatment reimbursement criteria at the time of the enrolment were included in the study. Therefore, some patients with no fibrosis or with early stage fibrosis may not have been treated. Thus, our results do not reflect the outcomes for CHC patients with an early stage of fibrosis. In addition, some eligible patients did not receive the treatment, which may have limited our analysis evaluating effects of the baseline characteristics on the SVR12 rates. Due to the observational nature of this study, many patients were not evaluated routinely during the treatment, and not all laboratory test results were available for all patients.

In conclusion, this observational study revealed that LDV/SOF, with or without ribavirin, for 12 or 24 weeks, yielded very high SVR12 rates, without any safety or concern for tolerability in Turkey. The effectiveness of the LDV/SOF treatment was not affected by the patient demographics or medical characteristics, such as the fibrosis level, cirrhosis status, previous treatment status, the HCV-RNA level, or HCV genotype.

Ethics Committee Approval: Ethics committee approval for this study was received from the Scientific Committee of the Ege University School of Medicine.

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception - T.Y., İ.T., G.E.; Design - F.G., H.P.; Supervision - N.P., N.G.U., R.U., M.T.; Materials - N.P., F.T.; Data Collection and/or Processing - O.R.S., T.Y.; Analysis and/or Interpretation - T.Y., O.R.S., H.P., U.S.A.; Literature Search - T.Y., İ.T., G.E., F.G., H.P.; Writing Manuscript - T.Y., İ.T., O.R.S., N.P., F.G.; Critical Review - T.Y., İ.T., O.R.S., N.D., R.U.

Acknowledgements: We thank Dr. Mehmet Berktas MD MSc MICR from Blue Idea Consulting London who provided data management, data analysis and editorial support.

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

Financial Disclosure: This study was supported by Gilead Sciences, Turkey for editorial support in the preparation of this manuscript.

REFERENCES

1. World Health Organization. Global Hepatitis Report 2017. Geneva; 2017.

2. Tozun N, Ozdogan O, Cakaloglu Y, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect 2015; 21: 1020-6. ***[Crossref]***

3. Kowdley K, Sundaram V. Role of ledipasvir/sofosbuvir combination for genotype 1 hepatitis C virus infection. Hepatic Med Evid Res 2016; 8: 75-80. ***[Crossref]***

4. Harvoni Summary of Product Characteristics [Internet]. 2017 [cited 2018 June 15]. p. 44. Available from: URL: http://www.titck.gov.tr/PortalAdmin/Uploads/KubKT/hTYrFiWZmySpW.pdf

5. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014; 370: 1889-98. https://doi.org/10.1056/NEJMoa1402454 ***[Crossref]***

6. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014; 370: 1483-93. ***[Crossref]***

7. Kowdley KV., Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014; 370: 1879-88. ***[Crossref]***

8. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015; 149: 649-59. ***[Crossref]***

9. Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: A multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis 2016; 16: 685-97. ***[Crossref]***

10. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness of ledipasvir/sofosbuvir in 4,365 treatment-naive, genotype 1 hepatitis C-infected patients. Hepatology 2016; 64: 405-14. ***[Crossref]***

11. Lim JK, Liapakis AM, Shiffman ML, et al. Safety and effectiveness of ledipasvir and sofosbuvir, with or without ribavirin, in treatment-experienced patients with genotype 1 hepatitis C virus infection and cirrhosis. Clin Gastroenterol Hepatol 2018: 16: 1811-9. ***[Crossref]***

12. Tapper EB, Bacon BR, Curry MP, et al. Real-world effectiveness for 12 weeks of ledipasvir-sofosbuvir for genotype 1 hepatitis C: The Trio health study. J Viral Hepat 2017; 24: 22-7. ***[Crossref]***

13. Russmann S, Grattagliano I, Portincasa P, Palmieri VO, Palasciano G. Ribavirin-induced anemia: mechanisms, risk factors and related targets for future research. Curr Med Chem 2006; 13: 3351-7. ***[Crossref]***

14. Yamazhan T, Kurtaran B, Esen B, et al. Effectiveness and safety of direct-acting antiviral therapies in treatment-experienced chronic hepatitis C infection patients in Turkey (HCV-8). Hepatol Int 2018; 12: 482-3.

15. Tabak F, Cuvalci NO, Kurtaran B, et al. Effectiveness and safety of direct-acting antiviral therapies in chronic hepatitis C infections patients with cirrhosis in Turkey (THU-374). J Hepatol 2018; 68: 297. ***[Crossref]***

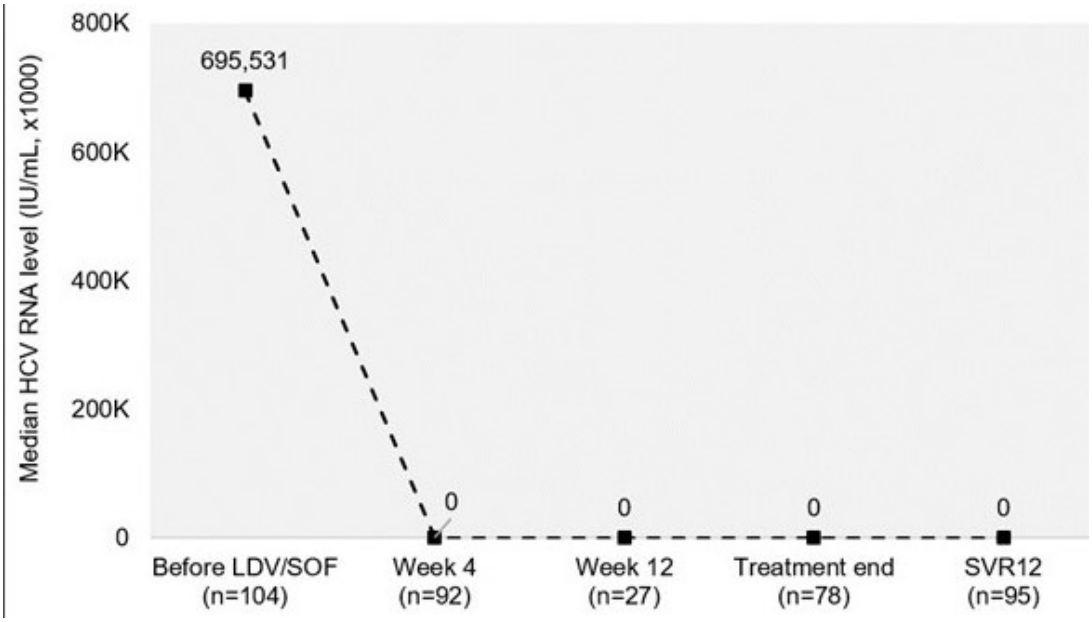
16. Idilman R, Demir M, Aladag M, et al. Recurrence and occurrence of hepatocellular carcinoma following ledipasvir and sofosbuvir treatment for chronic hepatitis C in patients with advanced liver disease: Turkish multicentre early access program (THU-381). J Hepatol 2018; 68(S1): 3017 ***[Crossref]***

17. Yaras S, Ucbilek E, Yilmaz I, Ozdogan O, Altintas E, Sezgin O. The real-life experience with directly acting antivirals in chronic hepatitis C treatment: A single center experience from Turkey (O-HCV-39). Hepatol Int 2018; 12(S2): 293.

18. Yoruk G, Ince N, Kurtaran B, et al. Effectiveness and safety of direct-acting antiviral therapies in chronic hepatitis C infection patients with diabetes mellitus in Turkey. Hepatol Int 2018; 12(S2): 488-89

19. Akhan S, Sayan M, Cakiroglu S, Gunes EV. Real-life data on interferon (IFN)-free direct acting antiviral (DAA) therapies for chronic hepatitis C (CHC) in Kocaeli (HCV-65). Hepatol Int 2018; 12(S2): 508.

20. Kandemir Ö. Chronic Hepatitis C Treatment with New Antiviral Agents. Mediterr J Infect Microb Antimicrob 2018; 7: 9. ***[Crossref]***



Supplementary Figure 1. The median HCV-RNA level.