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Real-Life Data of Chronic Hepatitis C Patients Treated with Direct-Acting Oral Antivirals: A Single-Center Study

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ABSTRACT

Introduction: Chronic hepatitis C virus (HCV) infection is one of the important causes of liver cancer and cirrhosis all over the worldwide.

Methods: The data of the patients diagnosed with chronic hepatitis C infection who applied to the Adult Infectious Diseases and Clinical Microbiology Outpatient Clinic of Erzincan Binali Yildirim University, Mengücek Gazi Training and Research Hospital were retrospectively analyzed. Accordingly, 51 patients treated with direct-acting oral antiviral drugs (DAAs) between January 2016 and May 2021 were included in the study. Patients whose treatment is still ongoing, whose treatment was completed but did not come to the 12th week after treatment, or whose control time has not yet come, were excluded from the study.

Results: It was observed that 58.8% of the cases participating in the study were male, 80.4% were infected with genotype 1b, and 74.5% were treatment-naive. When the treatment regimens used in the cases were examined, glecaprevir/pibrentasvir in 7.8%, sofosbuvir (SOF)/ledipasvir (LED), SOF/LED/ribavirin, and SOF/ribavirin in 15.7%, ombitasvir (OBV)/paritaprevir (P)/ritonavir (R)/dasabuvir and OBV/P/R/ribavirin in 76.5% (n=39) appears to be used. A statistically significant difference was found between the alanine aminotransferase, aspartate aminotransferase measurements, and platelet counts of the subjects participating in the study at the beginning, at the 4th week, at the end of the treatment, and at the 12th week (p=0.001). In these cases, a sustained virological response was achieved in 100%. In the follow-up of the cases, no serious side effects that required drug discontinuation were observed.

Conclusion: Our study showed that the treatment success of DAAs is 100% and their side-effect profiles are good.

Keywords: Chronic hepatitis C, DAA, SVR

Introduction

Chronic hepatitis C virus (HCV) infection is still one of the important causes of liver cancer and cirrhosis all over the worldwide. Approximately 71 million people have chronic HCV infection according to the World Health Organization's (WHO) latest data. According to the 2016 data of the WHO, approximately 399,000 people died from hepatitis C-related complications (1,2).

According to a study conducted recently, anti-HCV seropositivity was found to be around 1% in our country. Although the most common HCV genotype in the world is genotype 1, genotype 3, genotype 2, genotype 4, genotype 6, genotype 5, genotype 7, and genotype 8 infections are also seen, respectively. In our country, genotype 1 is the most common, and genotype 1b is the subtype (3-6).

Although the combination of pegylated interferon (PEG-IFN) + ribavirin was used in the treatment before, this combination has been replaced by direct-acting oral antiviral drugs (DAA) recently. A sustained virological response (SVR) of over 95% is achieved with the use of DAAs (7-11).

Our aim is to evaluate the chronic HCV patients who were treated with DAAs at our center in this study.

Methods

This study is a retrospective, cross-sectional study and was conducted with the approval of the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (approval number: 08/06, date: 21.06.2021).

The files of the patients diagnosed with chronic HCV infection who applied to the Adult Infectious Diseases Outpatient Clinic of Erzincan Binali Yildirim University, Mengücek Gazi Training and Research Hospital were retrospectively analyzed. Accordingly, patients treated with DAAs between January 2016 and May 2021 were included in the study. Patients whose treatment is still ongoing, whose treatment was completed but did not come to the 12th week after treatment, or whose control time has not yet come, were excluded from the study.

Demographic, clinical, and laboratory data of the patients, whether they had received treatment before, whether they had relapsed or not were

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obtained from the outpatients clinic patient registry files. Complete blood count, biochemical tests, and HCV-RNA levels were evaluated before the treatment, at the 4th week of the treatment, at the 8th week of the treatment, and at the end of the treatment. Genotype results were obtained from the patient files. The HCV-RNA level at the 12th week after the treatment was used in the evaluation of SVR.

HCV-RNA was studied using the COBAS TaqMan real-time polymerase chain reaction (RT-PCR) (Roche, Switzerland) assay. For HCV genotyping, RT-PCR and DNA sequencing were performed for the 5'UTR region of the HCV genome. Analysis of PCR products was performed using the ABI Prism 3130xl DNA Sequencer (Thermo Fisher Scientific, USA) instrument and the HVC Databank (http://hcvdb.org). Complete blood count was measured on a Sysmex XN-1000 Hematology System (Sysmex Corporation, Kobe, Japan) automated blood count device. Biochemical tests were measured on an AU 5800 (Beckman Coulter, California, USA). Alpha fetoprotein was measured by an immunoassay (Centaur XPT, Siemens Healthcare, Germany). Coagulation tests were measured by the turbidimetric method in the Celeron® alpha (Diapharma Group, Ohio, USA) device.

Statistical Analysis

The NCSS 2007 (Kaysville, Utah, USA) program was used. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used in the evaluation of the research data. The Shapiro-Wilk test and graphical examinations were used to confirm the quantitative data to the normal distribution. A repeated measure of variance analysis was used for within-group comparisons of normally distributed quantitative variables. To evaluate pairwise comparisons Bonferroni-corrected pairwise assessments were used. The Friedman test was used for intragroup comparisons of quantitative variables that did not show a normal distribution, and the Wilcoxon signed-rank test with Bonferroni correction was used for evaluating pairwise comparisons. A $p<0.05$ was considered statistically significant.

Results

The study was performed between January 2016 and May 2021 at Erzincan Binali Yildirim University, Mengücek Gazi Training and Research Hospital with 51 patients, 41.2% (n=21) female and 58.8% (n=30) male. The ages of the patients ranged from 23 to 86 years, with a mean age of 59.94±14.54 years. The HCV-RNA levels of the cases ranged from 5,104 IU/mL to 4,378,000 IU/mL, with a mean of 985,576.89±1,157,972.49.

When the genotype distribution of the cases is examined, it is seen that 80.4% of them are infected with genotype 1b, 5.9% with genotype 1a, 2% with genotype 2, 9.8% with genotype 3, 2% with genotype 4.

It was observed that the treatment status of 25.5% of the cases was treatment-experienced and 74.5% of them were treatment-naive. When the treatment regimens used in the cases were examined, glecaprevir/pibrentasvir in 7.8%, sofosbuvir containing regimens in 15.7%, ombitasvir (OBV)/paritaprevir (P)/ritonavir (R)/dasabuvir in 76.5% (n=39) and OBV/P/R/ribavirin appeared to be used. It was observed that 62% of the cases had co-morbidities such as diabetes mellitus, essential hypertension, and chronic renal failure. While co-infection was not observed in 94.1% of the cases, HBV co-infection was observed in 3.9% and HIV in 2% (Table 1).

Table 1. Demographic and clinical ınformation of the patients

Age, n (%)	**Mean ± SD**	**59.94±14.54**
	Median (min.-max.)	**64 (23-86)**
Gender, n (%)	Female	21 (41.2)
	Male	30 (58.8)
HCV-RNA levels (IU/mL)	Mean ± SD	985,576.89±1,157,972.49
	Median (min.-max.)	451,200 (5104-4,378,000)
Genotype distribution, n (%)	1a	3 (5.9)
	1b	41 (80.4)
	2	1 (2)
	3	5 (9.8)
	4	1 (2)
Treatment status, n (%)	Experienced	13 (25.5)
	Naive	38 (74.5)
Treatment regimen, n (%)	Glecaprevir/pibrentasvir	4 (7.8)
	SOF/LED, SOF/LED/ribavirin ve SOF/ribavirin	8 (15.7)
	OBV/P/R/D ve OBV/P/R/ribavirin	39 (76.5)
Co-morbities, n (%)	No	19 (38)
	Yes	31 (62)
Co-infection, n (%)	No	48 (94.1)
	HBV	2 (3.9)
	HIV	1 (2)

HCV: Hepatitis C virus, SOF: Sofosbuvir, LED: Ledipasvir, OBV: Ombitasvir, P: Pariteprevir, R: Ritonavir, PROD: Ombitasvir/pariteprevir/ritonavir/dasabuvir, HIV: Human immunodeficiency virus, SD: Standard deviation, min.: Minimum, max.: Maximum

Table 2. Change in laboratory values of patients completing treatment

		Beginning	Week 4	End of treatment	Follow-up week 12	p
ALT (IU/mL)	Mean ± SD	64.65±67.64	16.25±13.41	15.09±6.83	15.22±5.72	[b]**0.001****
	Median (Min.-Max.)	45 (10-401)	13 (5-79)	14 (4-36)	14 (5-32)	
AST (IU/mL)	Mean ± SD	51.26±37.56	18.82±6.09	20.53±10.21	19.37±6.62	[b]**0.001****
	Median (Min.-Max.)	37 (13-211)	18 (7-40)	19 (6-67)	18 (7-35)	
Hemoglobin (g/dL)	Mean ± SD	14.74±2	14.59±1.91	14.32±1.94	14.45±1.93	[c]**0.062**
	Median (Min.-Max.)	15 (8.9-19.6)	15 (9.7-18.2)	14.5 (9.1-19)	14.8 (9.1-18.5)	
Absolute neutrophil count (/mm^3)	Mean ± SD	3875.29±1298.56	4280±1975.18	4112.98±1580.56	3988.24±1482.64	[b]**0.518**
	Median (Min.-Max.)	3680 (1580-8350)	4130 (2210-11770)	3800 (1440-8900)	3550 (1500-8850)	
Platelet count*10^3 (/mm^3)	Mean ± SD	211.47±85.38	235.18±90.92	229.98±74.04	225.19±84.04	[b]**0.001****
	Median (Min.-Max.)	206 (179-564)	218 (102-683)	220 (97-578)	220 (200-583)	
HCV-RNA (IU/mL)	Negative		47 (92.2)	47 (100)	51 (100)	
	Positive		4 (7.8)	0 (0)	0 (0)	

[b]Friedman's test, [c]Repeated Measures test, **p<0.01, SD: Standard deviation, Min.: Minimum, Max.: Maximum, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HCV: Hepatitis C virus

There was a statistically significant difference between the alanine aminotransferase (ALT) measurements at the beginning, at the 4th week, at the end of the treatment, and at the 12th week of the subjects participating in the study (p=0.001). Decreases in the baseline ALT measurement at week 4, at the end of treatment, and at week 12 were significant (p=0.001; p=0.001; p=0.001).

There was a statistically significant difference between the aspartate aminotransferas (AST) measurements of the subjects at the beginning, at the 4th week, at the end of the treatment and at the 12th week of follow-up (p=0.001). Decreases at the 4th week, at the end of the treatment, and at the 12th week were significant compared with the initial AST measurement (p=0.001; p=0.001; p=0.001).

There was a statistically significant difference between the platelet count measurements at the beginning, at the 4th week, at the end of the treatment, and at the 12th week of follow-up (p=0.001). The increases in the measurement of the initial platelet count at the 4th week, at the end of the treatment, and at the 12th week were significant (p=0.001; p=0.001; p=0.001) (Table 2).

No side effects required discontinuation of treatment in patients. Itching was observed in two patient; weakness, nausea, and swelling in the legs were observed in one patient each.

Discussion

Chronic HCV infection is still one of the major causes of cirrhosis and hepatocellular carcinoma. While the combination of PEG-IFN and ribavirin was used in the treatment before, DAAs are now used today (11). When the real-life data of patients treated with DAAs are examined, different rates are reported in studies conducted in our country and in the world. In the study by Aygen et al. (8), which they analyzed the data of 55 patients infected with genotype 4, 100% SVR was found in patients without cirrhosis, while this rate was found to be 88.9% in patients with compensated cirrhosis. In another study of Aygen et al. (9), which they analyzed the data of 862 patients infected with genotype 1 or 4, SVR was found to be 99.1%. Today, pangenotypic drugs are used and Su et al. (12) evaluated the real-life data of glecaprevir/pibrentasvir in a 90-patient study and found 97.7% SVR rate. In our study, 100% SVR was detected and this rate shows that DAAs are effective.

Studies have shown that liver functions begin to improve immediately in patients with SVR. In the study of Cheng et al. (13), it was shown that ALT and AST levels returned to normal with the detection of post-treatment response and SVR. Simultaneously, histopathological improvement has been shown in patients who underwent liver biopsy before and after treatment. Similarly, in the Taiwan cohort, it was emphasized that cirrhosis and cirrhosis-related complications decreased in patients with SVR (14). Again, similar studies have shown improvement in non-invasive serum biomarkers in patients with SVR (15-18). In our study, a statistically significant decrease in ALT and AST levels at the end of the treatment; a statistically significant increase was observed in platelet counts (p<0.01). It was observed that the improvement in ALT, AST, and thrombocyte levels of the patients continued after SVR was provided. This result shows that fibrosis improves with treatment. Simultaneously, it demonstrates the importance of ensuring that patients diagnosed with chronic HCV are identified as soon as possible and access to treatment. Because if the liver reserve is good before treatment, the risk of cirrhosis and hepatocellular carcinoma will be lower after treatment. Additionally, extrahepatic findings related to HCV will be prevented (11).

Real-life data show that DAAs have a good side-effect profile compared to PEG-INF + ribavirin. Generally, it has been reported that the side effects that require discontinuation of treatment are few (8,9,12). In our study, no side effects requiring discontinuation of treatment were observed in any patient, indicating that the side-effect profile of DAAs is good.

Study Limitations

The small number of patients in our study is a limitation of the study.

Conclusion

Our study showed that the treatment success of DAAs is 100% and their side-effect profiles are good. However, the small number of patients is a limitation of our study. Multicenter studies with large numbers of patients are needed.

Ethics Committee Approval: This study is a retrospective, cross-sectional study and was conducted with the approval of the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (approval number: 08/06, date: 21.06.2021).

Informed Consent: Retrospective study.

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