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Distribution of chronic hepatitis C genotype and evaluation of clinical factors affecting direct-acting antiviral treatment responses in the Western Black Sea Region, Turkey

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Abstract. – OBJECTIVE: Chronic Hepatitis C (CHC) is a substantial global public health issue with significant variation between countries because of the genotypic differences. A sustained viral response (SVR) is essential to reduce the complications associated with CHC and can be achieved in most patients *via* direct-acting antivirals (DAAs). The present study aimed at determining the genotype distribution in patients with CHC in our region and the SVR in DAA therapy patients.

PATIENTS AND METHODS: The study was conducted retrospectively on 272 patients treated with DAA between September 2016 and 2021. Data including demographic and clinical characteristics of the patients (HCV RNA level, genotype, hepatitis B and HIV serology, cirrhosis and decompensation, presence of hepatocellular cancer, degree of hepatosteatosis, previous anti-HCV treatment experience, comorbidities) were recorded. The study's primary endpoint was to determine the SVR at week 24.

RESULTS: Genotype 1 was the most common genotype (94.5%), with genotype 1b accounting for most patients (78%) among those. It was observed that the patients received Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir (OPRD) (47%), Ledipasvir/sofosbuvir (LDS) (38%), and Glecaprevir/pibrentasvir (GCP) (15%) as DAA treatment. SVR was observed in 92% (223) of the 240 patients at the end of 24 weeks. SVR-24 was significantly higher in the patient group with serum HCV RNA level ≤ 852.533 (p=0.002), in the hypertensive group (p=0.018), and without the psychiatric disease group (p<0.001).

CONCLUSIONS: A high rate of SVR-24 was achieved by DAAs in CHC patients, most of whom were genotype 1 in the Western Black Sea Region, Turkey. Also, high viral load, hypertension, and psychiatric disease affected SVR-24, and clinical factors, such as cirrhosis, cirrhosis complications, hepatosteatosis, and other comorbidities did not.

Key Words:
Chronic hepatitis C, Genotype, Sustained viral response, Direct-acting antiviral.

Introduction

Hepatitis C virus (HCV) is one of the most common causes of cirrhosis and hepatocellular cancer, and it is a substantial global public health issue. An estimated 71.1 million chronically infected patients have been reported, accounting for 1% of the global population[1]. The infection affects all regions, with significant variation within countries. The highest disease burden is in the Eastern Mediterranean Region and European Region[2].

HCV strains are classified into eight genotypes, named one to eight, differing from each other at 31-33% of nucleotide sites[3]. Globally, genotype 1 is the most common, accounting for 44 to 46% of all cases of HCV infection worldwide, followed by genotype 3 and then genotype 4 (8 to 15%), representing 25 to 30% of all cases[4]. While genotypes 1 and 3 are common worldwide, the most significant proportion of genotypes 4 and 5 is in lower-income countries[5]. In the most extensive multicenter study[6] conducted in our country, genotype 1 comprised 91.8% of all Chronic Hepatitis C patients (CHC), but there was no Western Black Sea data. However, the study was conducted on patients receiving PEG-IFN+ribavirin; related factors, such as genotype, HCV RNA levels, age, ethnicity, adiposity, fibrosis, and insulin resistance have affected SVR rates in patients in Turkey[6]. Currently, CHC is almost curable with direct-acting antiviral (DAA) treatments. The length of therapy and response rates still depend

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in part on the HCV genotype[7]. A detailed understanding of the regional HCV genotype distribution may lead to the development of specific national treatment strategies.

Patients who are cured from their HCV infection experience numerous health benefits, including a decrease in liver inflammation, regression of fibrosis in most cases, and resolution of cirrhosis in half. For this reason, it is essential to provide a sustained viral response (SVR) with treatment in people with chronic HCV infection[8]. Identifying patients at risk of treatment failure could lead to interventions that improve cure rates. The strongest predictors of DAA treatment failure were advanced age, hepatocellular carcinoma history, private (against government) insurance, advanced cirrhosis status, HCV genotype, levels, and viral load before treatment[9,10]. As far as we know, no study on the clinical factors affecting treatment success in the era of DAA has been found in our country.

The present study aimed at determining the genotype distribution in patients with CHC in our region and the SVR in DAA therapy patients. It was also aimed at finding the patient-related factors that can affect the success of DAA treatment.

Patients and Methods

The study was conducted retrospectively on 272 patients treated with DAA in Zonguldak Bulent Ecevit University Hepatology Clinic between September 2016 and September 2021. Data including demographic and clinical characteristics of the patients (HCV RNA level, genotype, hepatitis B and HIV serology, cirrhosis and decompensation, presence of hepatocellular cancer, degree of hepatosteatosis, previous anti-HCV treatment experience, comorbidities) were recorded from the hospital database. The study's exclusion criteria were: history of transplantation, malignancies other than hepatocellular cancer, immunosuppressive therapy, or autoimmune liver disease. Patients over 18 years of age were included in the study. At week 24 after treatment, sustained HCV RNA negativity was defined as a sustained viral response (SVR). The study's primary endpoint was to determine the SVR at week 24.

The study received approval from the Zonguldak Bülent Ecevit University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee. (Protocol No.: 2022/08, Approval date: 20/04/2022). The study protocol meets the 1964 Declaration of Helsinki's ethical principles.

Statistical Analysis

The statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean±SD or median with interquartile range (IQR). Statistical relationships between categorical data were made using the Chi-Square test. Receiver Operating Characteristics (ROC) curve analysis was used to determine the cut-off value in continuous variables. Statistical significance was determined at $p<0.05$.

Results

All 272 participants were Caucasians, with the majority being women (61%). The mean age of the patients was 67.7 years (±12.7). Genotype 1 was the most common (94.5%), with genotype 1b accounting for most patients (78%). 25% of the patients had previous PEG-IFN+Ribavirin treatment experience. It was observed that the patients received recitasvir/Paritaprevir/Ritonavir/Dasabuvir (OPRD) (47%), Ledipasvir/sofosbuvir (LDS) (38%), and Glecaprevir/pibrentasvir (GCP) (15%) as DAA treatment. SVR was observed in 92% (223) of the 240 patients at the end of 24 weeks. There were 32 patients whose SVR could not be determined due to discontinuation of follow-up or death. 32% of patients had obstructive pulmonary diseases, such as chronic obstructive pulmonary disease or bronchial asthma. A diagnosis of psychiatric illness was present in 22.4% (61 patients) of all CHC patients.

Of the patients, 40% were diabetic, 66% hypertensive, and 34% were cirrhotic. 44.5% of patients had hepatosteatosis (Grade 1: 77 patients, Grade 2: 36 patients, Grade 3: 8 patients), 12% of patients had cirrhosis decompensation due to ascites, and 6% of patients had hepatocellular cancer, 3% of the patients had HBV coinfection and two of them had HIV coinfection. Ascites was present in 33 of 39 patients with decompensated cirrhosis. There were 20 patients with portal hypertension bleeding and 16 with hepatic encephalopathy. Three patients were intravenous drug users (Table I). It was observed that SVR could not be obtained in one of them, and the others left the follow-up.

Serum HCV RNA levels were analyzed with the ROC curve to predict SVR-24. Cut-off value was determined as 852.533 (AUC=0.684, $p=0.01$). SVR-24 was significantly higher in the patient group with serum HCV RNA level ≤852.533. ($p=0.002$). SVR-24 rate was significantly high-

er in the hypertensive group (p=0.018) and the non-psychiatric group (p<0.001). It was observed that other clinical factors did not significantly affect SVR-24 (Table II).

Discussion

It was determined that the overwhelming genotype in CHC patients in our region was genotype 1 (94.5%), and SVR was observed in 92% (223/240) of the patients at the end of 24 weeks with DAA treatment. SVR could not be achieved in only 17 patients (approximately 6%) in the present study. Anti-HCV prevalence was around 1% in the TURHEP research, including 5,460 patients from Turkey's general population[11]. Achieving SVR in CHC patients is essential to prevent the development of cirrhosis or progression to HCC or liver failure and ultimately reduce liver-related mortality[12]. Cure rates of more than 90% have been documented in most phase III clinical trials using DAA therapy in CHC patients. Although real-life data in our country are quite limited, Şengel et al[13] demonstrated that CHC patients, most of whom were genotype 1, used DAA or pegylated interferon alfa 2b treatment in the Marmara region; 87% of the patients (112 patients) achieved a sustained viral response at the 24th week after treatment. However, clinical factors affecting SVR were not evaluated in that study. Although DAA was not used, Gurbuz et al[6] showed that SVR was achieved in 62.7% of 761 treatment-naive patients with peginterferon alfa plus ribavirin; the majority of them were infected with genotype 1 (91.8%) in Turkey.

In patients with CHC receiving sofosbuvir-based DAA therapy in Vietnam, SVR was achieved in only 71.5% of patients at the end of the 12th week. In addition, comorbidities such as diabetes and hypertension were evaluated in that study, and no difference was observed between patients who achieved SVR and those who did not[10]. In the present study, most of the patients (approximately 95%) consisted of genotype 1 patients, and the SVR rate was higher in the hypertensive group. SVR rates may differ due to genotype differences.

In a multicenter retrospective study[14] conducted in Brazil, the overall SVR was 92% with DAA treatment, similar to our study. Genotype 1 dominance (78.5%) was also pronounced, although not as much as our population. More than half of the patients were cirrhotic and experienced PEG-IFN.

Table I. Baseline characteristics of study participants (n=272).

	Cut Off	n	%
Age	≤69	139	51.1
	>69	133	48.9
Gender	Male	107	39.3
	Female	165	60.7
Treatment	GCP	40	14.7
	OPRD	128	47.1
	LDS	104	38.2
Genotype	1	28	10.3
	1a	16	5.9
	1b	213	78.3
	2	2	0.7
	3	11	4
	4	2	0.7
Treatment experience	Yes	67	24.6
	No	205	75.4
SVR-24	Yes	223	82
	No	17	6.3
	Unknown	32	11.8
Pulmonary Disease	Yes	86	31.6
	No	186	68.4
Coronary artery disease	Yes	64	2.5
	No	208	76.5
Congestive heart failure	Yes	27	9.9
	No	245	90.1
Hyperlipidemia	Yes	58	21.3
	No	213	78.3
	Unknown	1	0.4
Chronic renal failure	Yes	34	12.5
	No	237	87.1
	Unknown	1	0.4
Hypertension	Yes	179	65.8
	No	93	34.2
Diabetes mellitus	Yes	108	39.7
	No	164	60.3
Cirrhosis	Compensated	54	19.9
	Decompensated	39	14.3
	No	179	65.8
Ascites	Yes	33	12.1
	No	239	87.9
Portal hypertension bleeding	Yes	20	7.4
	No	252	92.6
Hepatic encephalopathy	Yes	16	5.9
	No	256	94.1
Psychiatric illness	Yes	61	22.4
	No	211	77.6
Intravenous drug addiction	Yes	3	1.1
	No	269	98.9
Steatosis	Yes	121	44.5
	No	151	55.5
Chronic hepatitis B	Yes	9	3.3
	No	256	94.1
	Unknown	7	2.6
HIV	Yes	2	0.7
	No	249	91.5
	Unknown	21	21
Hepatocellular cancer	Yes	16	5.9
	No	242	89
	Unknown	14	5.1

OPRD, Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir. GCP, Glecaprevir/pibrentasvir. LDS, Ledipasvir/sofosbuvir. SVR, sustained viral response

Table II. Relationship between demographic and clinical characteristics and SVR (Chi-Square tests).

		SVR-24 (n=223)		
		Yes	**No**	***p*-value**
Age	≤69	111 (89.5%)	13 (10.5%)	0.034
	>69	112 (96.6%)	4 (3.4%)	
Gender	Male	85 (95.5%)	4 (4.5%)	0.23
	Female	138 (91.4%)	13 (8.6%)	
Treatment	GCP	31 (100%)	0 (0%)	0.21
	OPRD	104 (92.9%)	8 (7.1%)	
	LDS	88 (90.7%)	9 (9.3%)	
Genotype	1	25 (92.6%)	2 (7.4%)	0.879
	1a	14 (100%)	0 (0%)	
	1b	173 (92.5%)	14 (7.5%)	
	2	2 (100%)	0 (0%)	
	3	7 (87.5%)	1 (12.5%)	
	4	2 (100%)	0 (0%)	
Treatment experience	Yes	59 (90.8%)	6 (9.2%)	0.429
	No	164 (93.7%)	11 (6.3%)	
Pulmonary disease	Yes	69 (94.5%)	4 (5.5%)	0.52
	No	154 (92.2%)	13 (7.8%)	
Coronary artery disease	Yes	56 (96.6%)	2 (3.4%)	0.21
	No	167 (91.8%)	15 (8.2%)	
Congestive heart failure	Yes	25 (100%)	0 (0%)	0.14
	No	198 (92.1%)	17 (7.9%)	
Hypertension	Yes	154 (95.7%)	7 (4.3%)	**0.018**
	No	69 (87.3%)	10 (12.7%)	
Hyperlipidemia	Yes	50 (96.2%)	2 (3.8%)	0.56
	No	172 (92%)	15 (8%)	
Diabetes mellitus	Yes	92 (94.8%)	5 (5.2%)	0.33
	No	131 (91.6%)	12(8.4%)	
Chronic renal failure	Yes	28 (100%)	0 (0%)	0.28
	No	194 (91.9%)	17 (8.1%)	
Cirrhosis	Yes	79 (94%)	5 (6%)	0.61
	No	144 (92.3%)	12 (7.7%)	
Ascites	Yes	25 (89.3%)	3 (10.7%)	0.42
	No	198 (93.4%)	14 (6.6%)	
Portal hypertension bleeding	Yes	15 (88.2%)	2 (11.8%)	0.43
	No	208 (93.3%)	15 (6.7%)	
Hepatic encephalopathy	Yes	13 (92.9%)	1 (7.1%)	0.99
	No	210 (92.9%)	16 (7.1%)	
Psychiatric illness	Yes	40 (76.9%)	12 (23.1%)	**<0.001**
	No	183 (97.3%)	5 (2.7%)	
Steatosis	Yes	100 (91.7%)	9 (8.3%)	0.51
	No	123 (93.9%)	8 (6.1%)	
HCV RNA load (IU/ml)	≤852.533	128 (97.7%)	3 (2.3%)	**0.002**
	>852.533	95 (87.2%)	14 (12.8%)	
Chronic hepatitis B	Yes	6 (85.7%)	1 (14.3%)	0.7
	No	215 (93.1%)	16 (6.9%)	
Hepatocellular cancer	Yes	13 (81.3%)	3 (18.7%)	0.12
	No	200 (93.5%)	14 (6.5%)	

OPRD, Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir. GCP, Glecaprevir/pibrentasvir. LDS, Ledipasvir/sofosbuvir. SVR, sustained viral response.

Approximately one-third of our patients had cirrhosis, and only 25% of the patients experienced PEG-IFN-based therapy in our study. In real-life data evaluating the efficacy of DAA in cirrhotic CHC patients, the overall SVR rate was 91.4%. In another study[15], it has been observed that the SVR rate was significantly higher in decompensated cirrhosis than in compensated cirrhotic patients. Unlike our study, cirrhosis and cirrhosis-related complications such as ascites, portal hypertension bleeding, hepatic encephalopathy, and hepatocellular cancer were found not to have a significant effect on SVR. Similarly, overall SVR with sofosbuvir-based regimens for treating HCV in the

real-life setting in Alaska Native/Native Americans was 95.2% independent from HCV genotype or cirrhosis status[16]. However, in 1933[17], chronic HCV genotype 4 infected Egyptian patients who completed treatment with six different DAA regimens; SVR was strongly associated with cirrhosis and its degree. These differences may be due to the dominant genotype difference.

Considering intravenous drug use among the transmission routes of hepatitis C, the fact that there were only three patients with intravenous drug addiction in our study could be related to the relatively old age of our patient group (mean age was 67.7 years). The success of SVR-24 was significantly lower in patients with psychiatric diseases in our study. Interestingly, in a study[18] evaluating CHC patients' completion of treatment and their return for the SVR-12 test, it was concluded that the presence of psychiatric illness and substance abuse did not affect these parameters. Moreover, another study by Nabulsi et al[9] showed that these two patient-related parameters did not predict treatment failure. Although the number of our patients with intravenous drug addiction was only three, SVR could not be evaluated because two patients left the follow-up. It has been shown[19] that these patients have a high rate of discontinuation of treatment but higher rates of SVR in those who completed the treatment. All 61 patients with psychiatric illnesses in our study participants had at least one psychiatric drug use history. Among the reasons for the lower rate of SVR in this patients' group, drug-drug interaction or non-compliance with treatment that patients hide from the physician might be relevant.

In the present study, the SVR rate was also higher (97.7%) in patients with a low viral load than in those with a higher viral load (87.2%) (p=0.002). The low viral load has also been related to a higher SVR in CHC patients, 94% of whom are genotype 3[20]. Although the number of patients in whom SVR-24 was achieved in patients without hepatosteatosis was numerically higher than in patients with hepatosteatosis, statistical significance was not demonstrated in our study. Under PEG-IFN plus Ribavirin-based CHC treatment, a higher baseline HCV-RNA burden and a higher degree of steatosis have been shown[21] to be associated with lower SVR. To the best of our knowledge, the effect of hepatosteatosis on the treatment response of CHC patients receiving DAA therapy has not been investigated yet. In PEG-IFN plus Ribavirin-based CHC therapy, baseline HCV-RNA and the degree of steatosis have been shown to be associated with SVR. Still, the effect of hepatosteatosis on the treatment response of CHC patients receiving DAA therapy has not been investigated. This is the first study in our country evaluating genotype distribution and SVR-24 ratios and clinical parameters affecting SVR-24 in CHC patients in the Western Black Sea Region.

Limitations

The most important limitation of our study is that it was retrospective. The number of patients was insufficient to analyze clinical factors, such as HBV/HIV coinfection. Also, it was a single-center experience that prevented the results from being generalizable.

Conclusions

We evaluated the CHC genotype distribution, SVR rates at the end of the 24th week in patients who received new DAA, including OPRD, GCP, and LDS in the last five years, and clinical factors affecting this success in patients who received SVR in our region. Genotype 1 was the most common (94.5%), with genotype 1b accounting for most patients (78%). SVR was observed in 92% of the patients who received OPRD, LDS, or GCP at the end of 24 weeks. While the success of SVR was higher in hypertensive patients, it was lower in those with psychiatric disease and high viral load. It was observed that clinical factors such as cirrhosis and cirrhosis complications, hepatosteatosis, and other comorbidities did not affect SVR.

Ethical Approval

The study received approval from the Zonguldak Bülent Ecevit University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee. (Protocol No: 2022/08, Approval date: 20/04/2022). The study protocol meets the 1964 Declaration of Helsinki's ethical principles.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Authors' Contributions
ZGS and ID: Concept and design of study or acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be published.

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