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Early Viral Kinetics in Patients with Chronic Hepatitis C Treated with Direct-Acting Antivirals

Direkt Etkili Antivirallerle Tedavi Edilen Kronik Hepatit C Tanılı Hastalarda Erken Viral Kinetiğin Tayini

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ABSTRACT

Objectives: We aimed to determine parameters affecting viral kinetics among the first case series of chronic hepatitis C treated with direct-acting oral antiviral drugs in a tertiary university hospital and thus contribute to real-life data on direct-acting antiviral (DAA) treatments.

Materials and Methods: This is a prospective observational study that enrolled patients with chronic hepatitis C infection who were followed up between 2017 and 2019 and administered DAA treatment. Hepatitis C virus (HCV)-RNA (real-time polymerase chain reaction) was detected in the plasma samples of the patients before treatment (day 0) and on the 3rd and 7th days of treatment. Test results below 35 IU/mL were considered negative.

Results: The paritaprevir/ritonavir/ombitasvir/dasabuvir regimen was administered to 21 (44%) patients, sofosbuvir-based regimens to 28 (54%) patients, and glecaprevir-pibrentasvir treatment to 1 (2%) patient. HCV-RNA was detected to be negative significantly earlier in younger patients (p=0.005). The median disease duration was 7 years (range: 2-10), and viral clearance was obtained significantly earlier (p=0.038) in patients with a longer disease duration. The median initial viral load was 3,079,870

ÖZ

Amaç: Üçüncü basamak bir üniversite hastanesinde direkt etkili oral antiviral ilaçlarla tedavi edilen kronik hepatit C'li ilk olgu serilerinde viral kinetikleri etkileyen parametreleri belirleyerek direkt etkili antiviral (DAA) tedavilere ilişkin gerçek yaşam verilerine katkıda bulunmayı amaçladık.

Gereç ve Yöntemler: Bu çalışma prospektif gözlemsel nitelikte olup, 2017-2019 yılları arasında takip edilen, kronik hepatit C tanılı, DAA tedavi başlanması planlanan gönüllü hastalar ardışık şekilde dahil edildi. Tedavinin 0. 3. ve 7. günlerinde plazmada hepatit C virüs (HCV)-RNA çalışıldı. Gerçek zamanlı-polimeraz zincir reaksiyonu platformu olarak COBAS TaqMan HCV test (versiyon 2.0, Roche Molecular Systems, ABD) kullanıldı.

Bulgular: Çalışmaya alınan 50 hastadan 28'i (%56) kadın, yaş ortalaması 58±12,84 idi. Hastalardan 21'ine (%44) paritaprevir-ritonavir-ombitasvir-dasabuvir, 28'ine (%54) ise sofosbuvir içeren ilaçlar, 1'ine (%2) glecaprevir-pibrentasvir tedavisi verildi. Yaşı daha genç olanlarda (p=0,005) ve hastalık süresi daha uzun olanlarda (p=0,038) viral klirensin daha erken sağlandığı saptandı. Başlangıç viral yükü ortancası 3.079.870 IU/mL idi, viral klirensin sağlanma

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(range: 650,925-5,973,029) IU/mL, and no statistically significant correlation was found between the time to negative viral load and initial viral load (p=0.208).

Conclusion: Patients of younger ages and those with a history of longer disease durations became negative earlier, within the first days of treatment. No significant correlation was detected between the initial viral load and early viral kinetics.

Keywords: Viral hepatitis, viral kinetics, hepatitis C, direct-acting antivirals, viral load

süresiyle başlangıç viral yük arasında istatistiksel olarak anlamlı ilişki saptanmadı (p=0,208).

Sonuç: Tedavi sırasında viral yükü erken negatifleşen hastaların daha genç ve hastalık süresi daha uzun olanlar olduğu ortaya çıkmıştır. Başlangıç viral yükle erken viral kinetik arasında ilişki saptanmadı.

Anahtar Kelimeler: Viral hepatitler, viral kinetic, hepatit C, direkt etkili antiviraller, viral yük

Introduction

Chronic hepatitis C continues to be a major public health problem. It is estimated that 58 million people worldwide live with hepatitis C, an average of 1.5 million people are newly infected with chronic hepatitis C annually, and more than 1 million deaths occur each year due to complications of chronic viral hepatitis, including liver cancer and cirrhosis (1).

Hepatitis C virus (HCV) infection (mostly genotype 1) is reported to be responsible for 25% of cases of cirrhosis, 25-30% of hepatocellular carcinoma (HCC), and nearly half of the cases of liver transplantations performed in our country (2).

If left untreated, approximately 80,000 people will develop HCV-related cirrhosis, 3,770 people will develop HCC, and 3,420 people will die from HCV complications in 2030 (2).

Interferon-based regimens were effective in less than half of the cases, despite their long duration of use and serious side effects. Direct-acting oral antiviral drugs, first approved by the FDA in 2011 (3), completely changed hepatitis C treatment, with cure rates over 95%. New drugs were approved over the years, some of which came into use in Turkey after being reimbursed in 2016 (4).

Detection of blood HCV-RNA levels by real-time polymerase chain reaction (PCR), which is the most valid diagnostic tool, is also the most reliable method for monitoring treatment responses.

Although it is well known that direct-acting oral antivirals reduce HCV-RNA levels to an undetectable level in a very short time, there is not enough real-life data on how viral kinetics progress in the early post-treatment period. In this study, we detected HCV-RNA levels before (0^{th} day), on the 3^{rd}, 7^{th} and 90^{th} days of treatment and correlated these results with the alanine aminotransferase (ALT) normalization process (1^{st}, 4^{th}, 12^{th}, and 24^{th} week ALT levels). We aimed to establish real-life data regarding viral kinetic parameters as indicators of sustained viral responses and to contribute to creating up-to-date patient follow-up protocols in the era of direct-acting oral antiviral therapies in Turkey.

Materials and Methods

Patients

Fifty consecutive patients who had been diagnosed with chronic hepatitis C due to HCV-RNA positivity for over six months were planned to undergo direct-acting antiviral (DAA) treatment at the infectious diseases and clinical microbiology outpatient clinic, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine. Informed consent to participate in the prospective observational study was obtained from all patients.

Patients below 18 years of age, pregnant women, those unavailable for consecutive blood test controls, and those who did not give informed consent were excluded.

Methods

Peripheral blood samples obtained from patients via 10 cc EDTA tubes on days 0, 3, and 7 were centrifuged for 10 min at 2000 rpm, and plasma samples were then transferred to 3 separate Eppendorf (1.5 mL) tubes. Samples were stored at -80 degrees celcius until molecular testing. HCV-RNA levels were detected using the RT-PCR method and <35 IU/mL results were accepted as negative (Table 1). The RT-PCR platform COBAS TaqMan HCV Test (version 2.0, Roche Molecular Systems, USA) was used for plasma HCV-RNA detection.

The following data were also retrieved from outpatient case files: HCV-RNA levels detected at first admission or routine monitoring, HCV-RNA levels detected at 3, 6, and 12 months after treatment completion, and routine follow-up data. The parameters to be evaluated in the study were age, gender, comorbidities, infection duration, previous treatment or naivety, viral genotype, treatment modality and duration, biochemical [ALT, aspartate aminotransferase (AST), total bilirubin, alpha-feto-protein], hematological (complete blood count), coagulometric tests (prothrombin time, international normalized ratio), histopathological (liver biopsy), and ultrasound (US) findings.

Treatment success was defined as undetectable HCV-RNA levels (<35 copies/mL) three months after treatment completion and sustainable viral response. Rapid viral response was defined as undetectable HCV-RNA levels at week four. Recurrence was defined as the re-positivity of HCV-RNA within the following period after successful suppression at the end of treatment.

Patients were divided into three groups according to the viral load's negativity detection time.

Group 1: HCV-RNA negatives on 3^{rd} day,

Group 2: HCV-RNA negatives on 7^{th} day,

Group 3: HCV-RNA negatives on 4^{th} week.

The three groups were compared in terms of demographic, virologic (baseline viral load), biochemical, hematological, and histopathological data, duration of disease, receipt of previous inter quartile range-based treatment, and response to DAA drugs according to preferred modalities.

Table 1. Patients' HCV-RNA results during treatment.

Patient no	HCV RNA levels (IU/mL)			
	day 0	3rd day	7th day	Week 4
1.	170160	2 821	51	Negative
2.	667288	175,3	Negative	Negative
3.	115057	Negative	Negative	Negative
4.	497847.6	431.4	0.4	
5.	330 7016	3257.3	581.9	Negative
6.	2533 5572	1106.8	161.9	Negative
7.	1204 573	305.6	2.9	Negative
8.	545816.4	435.1	132.9	Negative
9.	3156376.9	47	Negative	Negative
10.	49 2120	66.2	59.7	Negative
11.	1359400.1	13.6	5.2	Negative
12.	3290 725	1085.6	17.7	Negative
13.	930209.3	163.1	0.1	Negative
14.	427119.8	296.6	2.3	Negative
15.	5540 190	5040.3	123.9	Negative
16.	69 06 16	97.1	11.2	Negative
17.	1152427.7	352.4	Negative	Negative
18.	3753603	145	Negative	Negative
19.	2060133.5	12.	Negative	Negative
20.	45 74 33	Negative	Negative	Negative
21.	14819597.7	4 330	23743.4	Negative
22.	256157.2	272.1	60.7	Negative
23.	5894 639	302:	Negative	Negative
24.	1049279.1	Negative	<35	Negative
25.	1572073.7	225.8	30.	Negative
26.	6208199.9	124.8	Negative	Negative
27.	4165828.3	0.4	28.3	Negative
28.	4741047.7	1600.7	<35	Negative
29.	7895 671	Negative	Negative	Negative
30.	2382.4	816.9	1 624	Negative
31.	8500571.1	1635.9	569	Negative
32.	11131113.1	487.6	2266.6	Negative
33.	1893169.1	211.2	11.3	Negative
34.	3003365	709.6	76	Negative
35.	5008178.8	15653.1	1 335	Negative
36.	12941.7	6203.5	4 599	Negative
37.	10612291.4	2155.3	567.4	Negative
38.	197155	2.3	Negative	Negative
39.	4764603.9	216.4	Negative	Negative
40.	1522195	10.5	Negative	Negative
41.	7 9 831	Negative	Negative	Negative
42.	2812415.5	Negative	Negative	Negative
43.	10497565.7	622.8	47	Negative
44.	5142276	Negative	Negative	Negative
45.	11181199.4	2431.3	266.4	
46.	712609.9	44.7	Negative	Negative
47.	5575319.1	Negative	Negative	Negative
48.	821735.9	7.5	Negative	Negative
49.	7058061.3	2274.6	813	Negative
50.	601835.6	1344.2	Negative	Negative

Statistical Analysis

Statistical analysis was performed using SPSS version 21. Descriptive analyses included data in percentage, frequency, mean ± standard deviation, median, and interquartile range. The distribution of continuous data was assessed using the Kolmogorov-Smirnov test, Shapiro-Wilk test, histogram, and Q-Q graph. For the qualitative variables, McNemar's test was used in the dependent groups, and for the independent groups, the Pearson chi-square test was used. The Pearson chi-square test was used in cases where the conditions cannot be met, and Fisher's exact test was used. For multiple comparison procedures for non-normally dispersed continuous data, the Mann-Whitney U test was used for Kruskal-Wallis and evaluated using the Bonferroni correction. The p-value was accepted as 0.05.

Results

Of the 50 patients included in our study, 28 (56%) were females with an average age of 58±12.84 years (Table 2). Among the

Table 2. Baseline characteristics of patients

Feature	n (%)
Age (mean ± standard deviation, years)	58±12.84
Gender (male/female, n, %)	28 (56%)/22 (44%)
Duration of illness (median, range)	7 years (2-10 years)
Genotype	
1b	39 (78)
1a	5 (10)
2a	2 (4)
3a	4 (8)
Treatment history	
Naive	18 (36)
Pegylated interferon/ribavirin	30 (60)
Sofosbuvir-ledipasvir/ribavirin	1 (2)
Not known	1 (2)
US findings	
Normal findings	27 (56.2)
Chronic liver disease	11 (22.9)
Compensated cirrhosis	8 (16.7)
Decompensated cirrhosis	2 (4.2)
Treatment regimens	
PrOD	14 (28)
PrOD/Ribavirin	7 (14)
SOF/LDP	13 (26)
SOF/LDP/Ribavirin	11 (22)
SOF/DAC	2 (4)
SOF/ribavirin	2 (4)
Glecaprevir-pibrentasvir	1 (2)
Histological Activity Index* (median)	6 (5-7)
Fibrosis score* (median)	3 (1-6)

*According to Modified Ishak's scoring system, PrOD: Paritaprevir/ritonavir/ombitasvir/dasabuvir, SOF: Sofosbuvir, DAC: Daclatasvir

patients, seven (14%) had chronic renal failure (CKF) and six (12%) had diabetes mellitus (DM). Ten (20%) patients were cirrhotic, while 40 (80%) were non-cirrhotic. No significant difference was detected in terms of treatment results between the genders.

By age comparison, younger subjects were found to have negative HCV-RNA levels significantly earlier (p=0.005). Compared among groups, between group 1 and group 3 (p=0.005), and between group 2 and group 3. Among the third group, age was statistically significant (p=0.007). Among the 2nd and 3rd groups, there was a significant age difference (p=0.30) (Table 3).

The median disease duration was 7 years, ranging from 2 and 10 years. For patients with longer disease duration, viral clearance was achieved significantly earlier (p=0.038). A statistically significant difference was detected in disease duration between group 1 and group 2 patients (p=0.014). The median disease duration of patients whose HCV-RNA was negative on the third day of treatment was 10 (6-14) years, and the median disease duration was 2 (1-9) years for those who had negative HCV-RNA on the seventh day, and 4 (3.25-11) years for the patients who were negative on the fourth week.

No significant difference was detected between the patients (n=30) who had a previous history of interferon-based therapy and naive patients (n=20) in terms of treatment outcomes (p=0.973).

In genotype distribution analysis, 39 patients (78%) were identified as genotype 1b. The average fibrosis score (F) of 21 patients who had undergone liver biopsy was determined as 3

Table 3. General characteristics of patients according to their group distribution

	Before treatment (day 0)	**HCV-RNA 3rd day negatives (n=13)**	**HCV RNA 7th day negatives (positive on 3rd day) (n=19)**	**HCV-RNA 4th week negatives (positive on 3rd and 7th days) (n=17)**	**p**
M/F ratio	22 of 28	7.6	6/13	8/9	0.417[a]
Age					
Mean ± SD Median (IQR)	58±12.84 58 (50.75-64.5)	51.31±14.82 52 (43.5-60.5)	56.42±7.66 57 (51-62)	66.06±11.88 64 (58.5-77)	**0.005[b]**
Disease duration[§] (years)	7 (2-10)	10 (6-14)	2 (1-9)	4 (3.25-11)	**0.038[b]**
Previous INF use (%)	30 (60%)	8 (61.5%)	11 (57.9%)	11 (64.7%)	0.973[a]
Genotype 1b ratio (%)	39 (78%)	12 (92.3%)	14 (77.8%)	13 (76.5%)	0.585[c]
Viral load[§] (IU/mL)	3,079,870.5 (650,925-5,973,029.25)	1,359,400 (381,375 -3,489,122)	3,156,376 (712,610-4,764,604)	5,008,179 (400,986.5-1,0554,928.5)	0.208[b]
HAI[§]	6 (5-7)	5.5 (4.5-6.25)	6 (5-8)	6 (5.5-9.5)	0.297[b]
Fibrosis score[§]	3 (1-6)	1 (0.75-3)	3 (2.5-4)	3 (1.75-5)	0,114[b]
ALT[§] (IU/L)	60.5 (33.75-75.5)	55 (27.5-97.5)	57 (29-73)	61 (38-76)	0,830[b]
AST[§] (IU/L)	45.5 (36.5-73.5)	38 (29.75-83.75)	42.5 (36-83)	54 (41-72)	0,399[b]
T. bilirubin[§] (mg/dL)	0.665 (0.53-0.797)	0.56 (0.34-1.035)	0.65 (0.49-1.05)	0.75 (0.63-0.79)	0,250[b]
WBC[§] (10^3/uL)	5 900 (5 100-7200)	6 500 (5 300-7100)	5 900 (5225-8235)	5 400 (4 930-6 335)	0,204[b]
HGB[§] (g/dL)	13.7 (12.47-14.7)	14.1 (12.15-14.75)	13.7 (13.2-14.1)	13.5 (11.05-14.57)	0,547[b]
PLT[§] (10^3/uL)	173,000 (120,500-217,500)	210,000 (155,500-257,000)	173,000 (81,000-220,000)	126,500 (74,250-195,250)	0,09[b]
Treatment regimens					
PrOD (%)	21 (44%)	5 (23.8%) (5/21); (38.5%) (5/13)	8 (38.1%) (8/21); (44.4%) (8/19)	8 (38.1%); (47.1%)	0.893[a]
Sofosbuvir-based treatment (%)	28 (54%)	8 (29.6%); (61.5%)	11 (37%); (55.6%)	9 (33.3%); (52.9%)	0.893[a]
Glecaprevir-pibrentasvir	1 (2%)	0 (0%)	1 (100%); (5.3%)	0 (0%)	-

SD: Standard deviation, IQR: Inter quartile range, INF: Interferon, HAI: Hepatic Activity Index, PROD: Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir, [§]Median values are given (interquartile range), [a]Pearson chi-square test was used, [b]Kruskal-Wallis's test was used, Fisher's exact test was used

(range 1 to 6) and the histological activity index (HAI) was 6 (range 5 to 7) according to the modified Ishak scoring system. In this respect, no statistically significant difference was observed in the HCV-RNA-negative periods (p=0.297).

Abdominal ultrasonography (USG) was normal in 27 patients (56%), chronic liver disease was detected in 11 patients (22.91%), compensated cirrhosis was detected in 8 patients (16.66%), and decompensated cirrhosis was detected in 2 patients (4.16%). Two patients (4.16%) had no USG data.

Patients had mean levels of ALT 60.5 (range: 33.75 to 75.5) IU/mL, AST 45.5 (range: 36.5 to 73.5) IU/mL, and total bilirubin 0.665 (range: 0.53 to 0.797) mg/dL before treatment. Transaminase levels, which were above normal at the beginning, all returned to normal levels at the first week of treatment.

Twenty-one (44%) patients received paritaprevir+ritonavir+ombitasvir/dasabuvir, 28 (54%) patients received sofosbuvir (SOF), and 1 (2%) received glecaprevir-pibrentasvir. Treatment durations were 12 weeks for 44 patients (86%), 24 weeks for 6 patients (12%), and 8 weeks for 1 patient (2%).

Ribavirin was administered in 8 (38.1%) patients on paritaprevir/ritonavir/ombitasvir/dasabuvir (PrOD) and 12 (42.9%) patients receiving SOF. The bilirubin increase was not significant in both groups, with an average increase of 0.39 mg/dL at week 4 in the SOF group and an average increase of 0.065 mg/dL in the first week of treatment in the PrOD regime group, which was similar to baseline normal levels at week 4. Bilirubin changes were not related to the receipt of ribavirin.

A total of 33 adverse effects were recorded in 20 patients (40%), and fatigue was the most common (n=12). Others included itching (n=3), erythema (n=3), hyperbilirubinemia (n=3), dry cough (n=2), headache (n=2), heartburn (n=2), anemia (n=2), nausea (n=1), rash (n=1), hypersomnia (n=1), and weight loss (n=1). Adverse effects were similar in both treatment groups (p=0.458) and were observed more densely in the first weeks of treatment, with 11 patients experiencing multiple adverse effects.

The median initial viral load of the patients was 3,079,870 (650,925-5,973,029) IU/mL, and no statistically significant relationship was found between the negativity times and the initial viral load (p=0.208).

Plasma HCV-RNA levels were measured on days 0, 3, 7, 4, 12, and 24. On the third day of treatment, HCV-RNA was detected in 13 patients (22%). In 37 patients (78%), positive findings were observed. On the 3rd day, HCV-RNA was undetectable in 19 of 37 patients (38%) who were HCV-RNA positive and was recorded as positive in 18 patients (36%).

On the 7th day of treatment, HCV-RNA was negative in 32 patients (64%).

In 48 (96%) patients undergoing treatment, HCV-RNA levels were undetectable at week 4 (1 patient died, 1 patient lost to follow-up and therefore results could not be recorded at week 4, and later) and remained negative at week 12. Of the 44 patients treated for 12 weeks, 43 were found to be HCV-RNA-negative at week 24, whereas 1 patient was found to be positive and accepted as unresponsive.

In 47 (97.9%) patients who completed the treatment, a sustained viral response was obtained, and 1 (2%) patient showed no response.

The patient, who was 56 years old and had not received a response, was diagnosed with chronic hepatitis C (genotype 3a) for 4 years. She had decompensated cirrhosis and previously received interferon/ribavirin treatment. When she first received the treatment (SOF/ledipasvir/ribavirin), she could provide it at her own expense and use it for 12 weeks (treatment duration was not sufficient). The second time, the same treatment was administered for 24 weeks, and a sustained viral response was obtained. In both treatments, on days 3 and 7, the HCV-RNA levels of the patient were detectable. During the follow-up period, the patient developed HCC and was treated with chemoembolization and chemotherapy. The patient died during follow-up.

Eighteen patients had negative HCV-RNA levels at week 4, 8 of which were treated with SOF-based regimens and 10 were treated with PrOD. The mean age was 64 years; the mean duration of the disease was 4 (3.25-11) years, and 13 (72%) patients had previous treatment experience. Genotype 1b was the major genotype (n=13), and the remaining genotypes were 3a (n=3), and 1a (n=2). The mean HAI score was 6 (range: 5.5-9.5) over 18, and the fibrosis score was 3 (1.75-5) over 6. USG results of the patients showed findings of cirrhosis in 8, hepatic steatosis in 2, and chronic liver disease in 2. The accompanying comorbidities were DM (n=3), chronic hepatitis B (n=2), delta hepatitis (n=1), CKF (n=2), hypertension (n=2), hyperthyroidism (1), and chronic heart failure (1). The mean baseline viral load of this group was found to be 5,008,179 IU/mL (range: 400,986.5-1,0554,928.5) IU/mL. When comparing this group with those whose initial viral load was negative, no statistically significant difference was detected (p=0.097).

Discussion

This is one of the first studies in our region to focus on early viral kinetics in response to the treatment of chronic hepatitis C with DAAs. We achieved sustained viral response in 47 of 50 patients (97.9%) who were able to complete the treatment protocol. Our results are similar to those of other studies regarding the outcomes with DAAs (5). We found that patients with early viral load negativity had younger ages and longer mean disease durations.

Patients over 40 years of age reportedly have higher proportions of fibrosis (6). Older age has been associated with delayed viral clearance and suboptimal treatment responses (6). Earlier viral clearance in our relatively younger patients confirms the current data.

Despite the small number of patients, baseline viral load did not significantly affect early viral kinetics in our investigation. Using A. linear discriminant analysis technique. Garbuglia et al. (7) examined the potential relationship between sustained virologic response (SVR) and viral kinetics in 33 individuals with viral hepatitis C genotype 1. In their study, plasma HCV-RNA levels were assessed at days 0, 1, 2, 3, 4, 5, 14, 28 and weeks 8, 12, 24 of treatment as well as at weeks 8, 12, 16, 20, and 24 after completion of the

treatment protocol with telaprevir/peg-interferon/ribavirin. There was no significant difference in early viral kinetics between those who could or could not achieve SVR. Remarkably, there was no correlation between SVR and initial viral load, although this study included treatment options before DAA.

In line with some other studies, all patients receiving DAA had normalized ALT, AST, and total bilirubin levels in our cohort (8,9).

Patients whose viral loads did not become negative on the 3rd and 7th days but did so in the 4th week most frequently had DM as a comorbidity. Diabetes is associated with an accelerated progression of chronic hepatitis C-related liver damage and a delayed response to treatment (10,11).

Patients receiving pegylated interferon and ribavirin were separated into groups based on the HOMA index in a study by Desbois et al. (11). Early viral kinetics were assessed by assessing HCV-RNA levels at 48 h, 2, 4, and 12 weeks. It has been shown that insulin resistance impairs viral dynamics regardless of viral genotype and patient ethnic group (11).

Studies focusing on demonstrating early viral kinetics in patients treated with DAA are scarce. Balagopal et al. (12) investigated the relationship between early viral kinetics and liver histopathology in 6 treatment-naive, non-cirrhotic, HIV co-infected (ART suppressed) chronic hepatitis C patients receiving DDA (PrOD or PrOD/Ribavirin) and found 90% decrease in the numbers of infected hepatocytes within 1 week after treatment initiation, indicating a correlation between viral clearance and histopathological improvement (12).

Gambato et al. (13) we investigated early viral kinetics in DAA-treated patients with compensated cirrhosis. The goal of this study was to personalize treatment and reduce the time required to achieve a cure. Blood samples were collected from 74 patients with compensated cirrhosis who were administered DAA at the 4th hour, 8th hour, 24th hour, 2nd day, 3rd day, 4th day, 2nd week, 3rd week, and 4th week. A viral kinetic study was conducted. In the study, 68 patients (92%) were cured. The time required for HCV clearance was shorter in patients with a lower fibrosis score and lower initial viral load, and modeling studies have shown that determining the optimal duration in cirrhotic patients can reduce treatment costs by 40%.

Perpiñán et al. (14) collected blood samples from 71 HCV patients on DAA at the 4th hour, 8th hour, 1st day, 7th day, 2nd week to 4th week to study early viral kinetics. Cure was achieved in 63 of the patients (89%); seven of the eight patients who could not be cured had resistance-related genetic mutations (resistance-associated substitution) at the time of treatment or recurrence. This study demonstrates the significance of early viral kinetics in predicting DAA resistance.

Dahari et al. (15) investigated early viral kinetics in 58 chronic hepatitis C patients (57% of whom were cirrhotic) receiving various DAA regimens and used mathematical modeling to determine recovery time. In the study, in which a sustained viral response was obtained in 99% of the cases, modeling results revealed that 23 (43%), 16 (30%), 7 (13%), 5 (9%), and 3 (5%) patients were cured at the 6th, 8th, 10th, 12th, and 13th weeks of treatment, and shortening of the treatment duration was considered to be cost-effective.

Bertino et al. (16) used mathematical modeling to investigate the efficacy of short-term treatments in patients infected with genotype 1b who were treated with daclatasvir and asunaprevir. Blood samples were collected from patients just before treatment, at the 4th hour, 8th hour, 48th hour, 72nd hour, 1st week, 4th week, 24th week, and 12 weeks after treatment, and their HCV-RNA levels were measured. Of the 95 patients included in the study, 89 (94%) were cured. According to the modeling study, patients with HCV-RNA levels of 15 IU/mL on days 14 and 28 could achieve cure rates of 100% and 98.5%, respectively, with 6 and 8 weeks of treatment.

In the study conducted by Maasoumy et al. (17) including 298 patients, viral kinetics at weeks 0, 1, 2, 4, 8, 12, 16, 20, and 24 were evaluated with 4 different SOF-based treatment regimens. The likelihood of recurrence in genotype 3 patients was found to be significantly correlated with the high HCV RNA levels detected at the second week of SOF/RBV treatment.

While a shorter duration of disease was found to be a favorable factor for SVR with pegylated interferon + ribarivin treatment (18), we found the contrary with direct acting antivirals; the patient who achieved HCV-RNA negativity on the 3rd day of treatment had a longer duration of disease. The duration of the disease, either shorter or longer, has not been shown to be a predictive factor of response previously (19,20).

Conclusion

In our study, 47 of the 48 patients (97.9%) who successfully completed DAA treatment achieved SVR, with only one (2.08%) returning to positive 12 weeks after treatment and evaluated as relapse. However, he was cured after a 24-week re-treatment.

It was determined that patients with a younger age and longer disease duration had earlier viral clearance. However, no association was observed between the initial viral load and early viral kinetics.

Because the recurrence rate was so low (2.08%), no conclusions could be drawn regarding the relationship between early viral kinetics and recurrence frequency. Larger case series can reveal this relationship more clearly.

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Ethics

Ethics Committee Approval: The study was conducted with the approval of the Clinical Studies Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 231341/date: 16.06.2017).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.G., İ.İ.B., R.Ö., S.Y.K., B.M., N.S., Ö.F.T., Design: D.G., İ.İ.B., R.Ö., B.M., Ö.F.T., Data Collection or Processing: D.G., M.A.K.,

A.Ö., K.M., S.Y.K., B.M., G.A., Analysis or Interpretation: D.G., İ.İ.B., R.Ö., M.A.K., A.Ö., K.M., S.Y.K., R.K., G.A., Ö.F.T., Literature Search: D.G., R.Ö., N.S., Writing: D.G., İ.İ.B., R.Ö.

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