Official Journal of Erciyes University Faculty of Medicine

DOI: 10.14744/cpr.2025.33623
J Clin Pract Res 2025;47(3):309–315

Effectiveness and Safety of Glecaprevir/Pibrentasvir Combination Therapy in Patients Diagnosed with Chronic Hepatitis C

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Cite this article as:
Karabulut K, Aygen B, Yıldız O, Kahveci HN, Ture Z, Kalın Ünüvar G, Yüceil Karabulut A. Effectiveness and Safety of Glecaprevir/Pibrentasvir Combination Therapy in Patients Diagnosed with Chronic Hepatitis C. JClinPractRes2025;47(3):309–315.

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Submitted: 15.10.2024
Revised: 17.01.2025
Accepted: 03.06.2025
Available Online: 17.06.2025

Erciyes University Faculty of Medicine Publications - Available online at www.jcpres.com

ABSTRACT

Objective: The study aimed to evaluate the effectiveness and safety of glecaprevir/pibrentasvir (GLE/PIB) treatment in patients infected with hepatitis C virus (HCV).

Materials and Methods: Forty-four patients who applied to the Infectious Diseases and Clinical Microbiology Clinic between December 2019 and December 2022 were infected with HCV genotype 1–6 and came regularly for treatment and follow-up visits were included in the study. The study was conducted retrospectively by accessing patient data through the hospital information management system. In patients receiving GLE/PIB treatment, data regarding the effectiveness and reliability of the treatment were recorded both during the treatment process and after the treatment was terminated.

Results: Of the 44 patients, 47.7% were genotype 1b, 18.2% were genotype 1a, 15.9% were genotype 2, 13.6% were genotype 4, and 4.5% were infected with genotype 3. Early virological response (EVR) was achieved in 81.8% of 44 patients. End-of-treatment response and sustained virological response at the 12th week were achieved in all patients. No treatment failures were observed. There was no significant difference between EVR rates according to genotypes. There was a significant improvement in the liver function tests of the patients from the 4th week of treatment. The most common adverse events were fatigue and itching.

Conclusion: The GLE/PIB combination is an effective and safe treatment option in the treatment of HCV infection. Due to the high EVR rates, more comprehensive studies need to be conducted to keep the duration of GLE/PIB treatment shorter in some patient groups in patients diagnosed with CHC.

Keywords: Effectiveness, glecaprevir, hepatitis c, pibrentasvir, safety.

INTRODUCTION

Hepatitis C virus (HCV) infection leads to chronic liver disease, which causes significant mortality and morbidity. It is one of the leading causes of cirrhosis and hepatocellular carcinoma (HCC). It is estimated that there are nearly 70 million people infected with HCV worldwide. Although HCV infection is a treatable disease, a large number of patients cannot be diagnosed early due to the infection's ability to remain asymptomatic for a long time.[1] Approximately 20% of patients who cannot be treated develop cirrhosis within 30 years. It has been reported that in patients with cirrhosis, approximately 3–6% experience decompensation, and 1–5% develop liver failure each year.[2] To prevent these complications, it is necessary to treat HCV infection effectively and safely.

The purpose of this research is to assess the safety and effectiveness of the glecaprevir/pibrentasvir (GLE/PIB) combination, which is effective against all HCV genotypes in patients diagnosed with chronic hepatitis C (CHC).

KEY MESSAGES

- In all patients in our study, the SVR12 target has been achieved. Additionally, we support the idea of conducting new studies to shorten treatment duration for specific patient groups, given the very high EVR rates.
- With the initiation of treatment, a significant improvement has been observed in the liver function tests of the patients.
- No patients have discontinued their treatment due to adverse events, as the adverse events are extremely tolerable.

MATERIALS AND METHODS

The study included 44 patients who visited the Infectious Diseases and Clinical Microbiology Outpatient Clinic between December 1, 2019, and December 31, 2022, and who had used the GLE/PIB combination, were infected with HCV genotypes 1–6, and were followed up for chronic hepatitis C. The study was conducted retrospectively by accessing patient data through the hospital information management system. Data regarding the effectiveness and safety of treatment were examined in patients receiving GLE/PIB therapy both during the treatment process and after the treatment was discontinued. With the decision dated June 23, 2021, and with the number 2021/459, the Ethics Committee of the Faculty of Medicine at Erciyes University provided ethical permission for the study. This study was conducted in accordance with the Declaration of Helsinki.

Study Protocol

The demographic characteristics (age, gender) of patients treated with the GLE/PIB combination, their underlying diseases, whether they had prior treatment experience or were naive to treatment, antiviral treatment history in those who had experienced treatment, HCV genotype, and pre-treatment baseline HCV-RNA values were recorded. During the treatment and follow-up of the patients, complete blood counts, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and HCV-RNA values were examined at four-week intervals. Values were recorded before treatment, at the 4th and 8th weeks of treatment, and the 4th and 8th weeks of follow-up. The creatinine values were compared before treatment, after treatment, and at the end of the follow-up period. In the 4th week of treatment, HCV-RNA negativity was evaluated as an early virological response (EVR), HCV-RNA negativity at the end of treatment was considered as an end-of-treatment response (ETR), and HCV-RNA negativity at the 12th week of follow-up was assessed as a sustained virological response (SVR12). The criteria for treatment failure were considered to be non-response and relapse.

Statistical Analysis

IBM SPSS Statistics for Windows Version 22.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA) was used to analyze the data. The Kruskal-Wallis analysis was used to investigate the patients' measurements according to genotypes. The Mann-Whitney U test was used with corrections to determine which group caused the difference as a result of the Kruskal-Wallis analysis. The Friedman test has been applied to examine the measurements in terms of different times of the treatment process. The all-pairwise method has been used in pairwise comparison tests. A chi-square analysis was conducted for the ordinal evaluations. The McNemar test was used to see if there were any variations in HCV-RNA levels over time. Qualitative data is presented in percentages, while quantitative data is presented as median (min-max). The significance level has been set at $p<0.05$.

RESULTS

Demographic Data

As a result of screenings conducted through the hospital information management system, 56 patients have been identified for whom GLE/PIB treatment is planned. Two of these patients were denied the opportunity to participate in the trial because of refusal of treatment, two could not complete the treatment due to the pandemic, and one lost their life due to reasons related to malignancy during treatment. Seven of the 51 patients who completed their treatment were excluded from

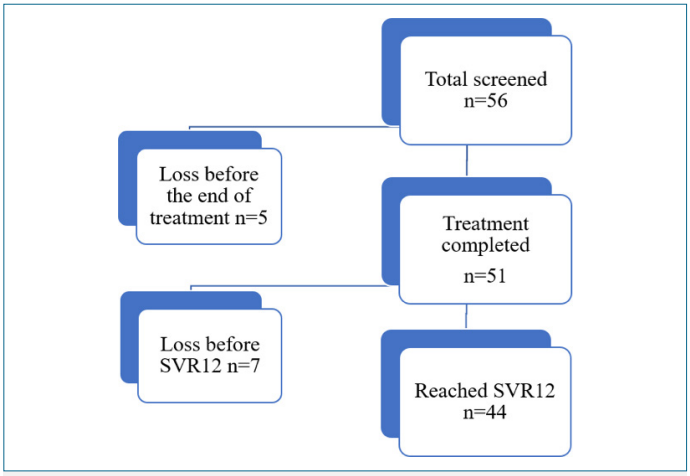

Figure 1. Flowchart.

SVR12: Sustained virological response at the 12th week.

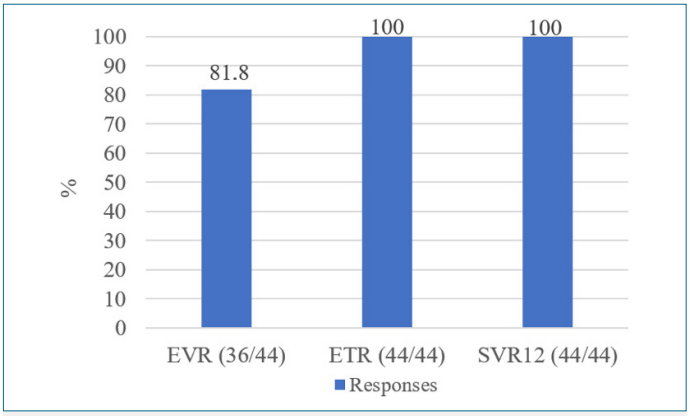

Figure 2. EVR, ETR, and SVR12 rates of patients achieved with treatment.

EVR: Early virological response; ETR: End-of-treatment response; SVR12: Sustained virological response at the 12th week.

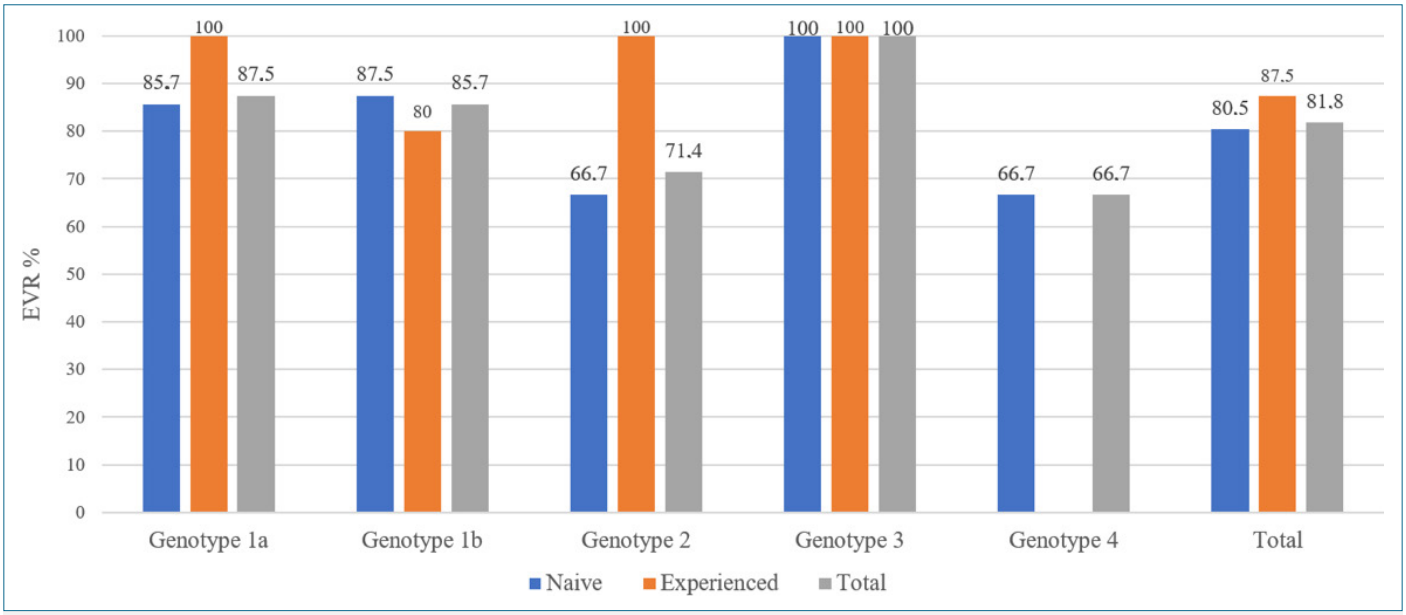

Figure 3. EVR rates according to patient genotype and treatment experience.

EVR: Early virological response.

the study due to irregular attendance at post-treatment check-ups, resulting in a total of 44 patients evaluated in the study (Fig. 1). In the study, 21 out of 44 patients (47.7%) were infected with genotype 1b, 8 (18.2%) with genotype 1a, 7 (15.9%) with genotype 2, 6 (13.6%) with genotype 4, and 2 (4.5%) with genotype 3. Of the patients, 23 (52.3%) were female and 21 (47.7%) were male. Out of a total of 44 patients, 36 were treatment-naive, and 8 were treatment-experienced. The treatment experiences of patients, categorized by their genotypes and other demographic characteristics, are summarized in Table 1.

Treatment Response

When examining the treatment responses of all patients in the study, it was found that EVR was observed at a rate of 81.8%, while ETR and SVR12 were observed at a rate of 100% (Fig. 2). No treatment unresponsiveness or relapses were detected in the patients. The EVR rates, according to patients' genotypes and treatment experiences, are shown in Figure 3.

In the study, since the ETR and SVR12 rates were 100%, EVR rates were used to evaluate treatment response based

Table 1. Demographic characteristics of patients

	Genotype 1a (n= 8)	Genotype 1b (n= 21)	Genotype 2 (n= 7)	Genotype 3 (n= 2)	Genotype 4 (n= 6)	Total (n= 44)
Male gender, n (%)	6 (75)	8 (38)	4 (57)	1 (50)	2 (33)	21 (48)
Age, year	59.5 (25–77)	66 (46–80)	66 (28–73)	39.5 (25–54)	49 (29–79)	63.5 (23–80)
Number of cirrhotic patients, n (%)	0	1 (4.7)	0	0	0	1 (2.2)
Treatment naive, n (%)	7 (87.5)	16 (76.2)	6 (85.7)	1 (50)	6 (100)	36 (81.8)
Treatment experienced, n (%)	1 (12.5)	5 (23.8)	1 (14.3)	1 (50)	0	8 (18.2)
Peg-IFN+RBV	0	5 (100)	1 (100)	1 (100)	0	7 (87.5)
Peg-IFN +RBV+ SOF/LDV	1 (100)	0	0	0	0	1 (12.5)
Comorbidities, n (%)						
CKD	2 (25)	9 (42.8)	3 (43.8)	2 (100)	2 (33.3)	18 (40.9)
Stage 1–2	2 (100)	4 (44.4)	1 (33.3)	1 (50)	0	8 (44.4)
Stage 3	0	1 (11.1)	2 (66.7)	0	0	3 (16.6)
Stage 4–5	0	4 (44.4)	0	1 (50)	2 (100)	7 (38.9)
DM	0	4 (19)	0	0	0	4 (9.1)
HT	2 (25)	6 (28.5)	0	0	2 (33.3)	10 (22.7)
Malignancy	0	2 (9.5)	0	0	1 (16.6)	3 (6.8)
Cardiac diseases	0	2 (9.5)	0	0	2 (33.3)	4 (9.1)
Thyroid diseases	0	0	1 (14.2)	0	0	1 (2.3)
Neurological diseases	0	1 (4.7)	1 (14.2)	0	0	2 (4.5)
IVDU	1 (12.5)	0	1 (14.2)	0	0	2 (4.5)
HCV-RNA (IU/ml), n (%)						
$\geq 10^6$	6 (75)	10 (47.6)	3 (42.8)	1 (50)	2 (33)	22 (50)
$<10^6$	2 (25)	11 (52.4)	4 (57.2)	1 (50)	4 (67)	22 (50)

Age values are given as median (min–max). IVDU: Intravenous drug user; DM: Diabetes mellitus; HT: Hypertension; CKD: Chronic kidney disease; Peg-IFN+RBV: Pegylated interferon + ribavirin; SOF/LDV: Sofosbuvir/ ledipasvir.

on demographic characteristics and comorbidities. When evaluating the EVR rates according to genotypes, no statistically significant difference was observed (p=0.39). While no significant difference was found in the SVR rates obtained according to patients' HCV-RNA levels, treatment experiences, and ages, it was determined that the rates of SVR varied according to their genders. The prevalence of EVR in female patients was found to be 91.3%, while in male patients, it was 71.4% (p=0.01). Patients were grouped according to their underlying conditions, and the EVR rates were examined, revealing no statistically significant difference between these rates (p>0.05) (Fig. 4).

Changes in Biochemistry and Complete Blood Count Parameters

The study found that the median ALT and AST levels at the 4th and 8th weeks of treatment and follow-up were significantly lower compared to the median ALT and AST levels before treatment (p=0.01) (Appendix 1).

It has been determined that there was no statistically significant change in the platelet counts of patients before and after treatment (p=0.34) (Appendix 1). When looking at the creatinine values, the median level before treatment was 0.72 (0.49–1.11) mg/dl, while at the end of treatment it was measured at a median of 0.79 (0.5–1.23) mg/dl, and follow-up, the median was 0.8 (0.53–1.1) mg/dl. This increase is statistically significant (p=0.01) (Appendix 1).

Adverse Events

Patients in the trial have not had any adverse effects that would force them to stop receiving medication. It has been observed that the rate of adverse events in patients after 4 weeks of medication use is 27.3%. It has been found that 13.6% of patients experienced fatigue, 11.4% had itching, 2.3% had rashes, 2.3% experienced weight gain, and 2.3% suffered from dyspepsia. It has been observed that the rate of adverse events in patients after 8 weeks of medication use

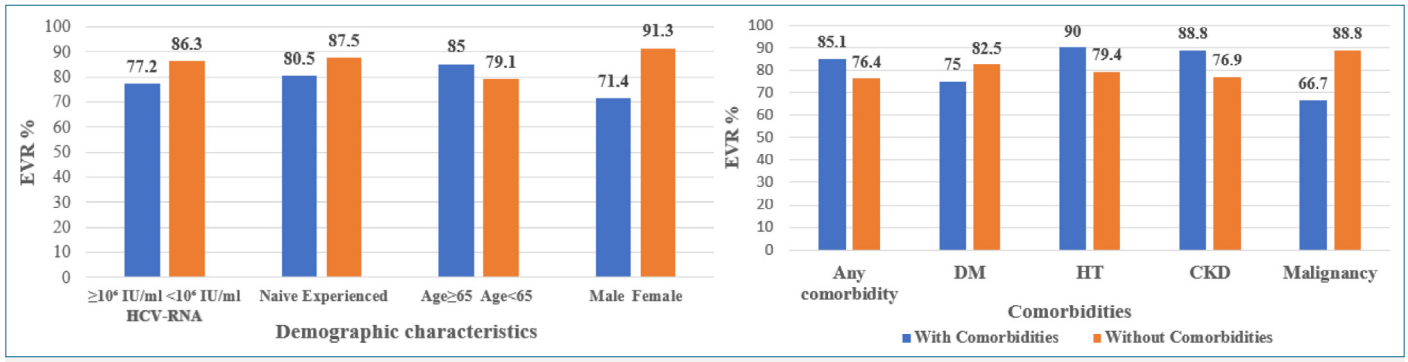

Figure 4. EVR rates according to demographic characteristics and comorbidities.

CKD: Chronic kidney disease; DM: Diabetes mellitus; EVR: Early virological response; HT: Hypertension.

is 20.5%. It has been observed that similar adverse events include itching (11.4%), fatigue (9.1%), weight gain (2.3%), and dyspepsia (2.3%).

DISCUSSION

CHC infection is a viral infection that can lead to serious complications such as cirrhosis, liver failure, and death. Efforts are being made to develop prevention, diagnosis, and treatment strategies for effective combat against HCV infection worldwide. In recent years, given the development of direct-acting antivirals with high efficacy and minimal adverse event profiles, it can be concluded that substantial advancements have been made in the treatment of HCV infection.[3–6]

As a result of studies conducted to discover new molecules for the treatment of HCV infection, the combination of the NS3/4A protease inhibitor GLE and the NS5A inhibitor PIB, which are newly developed drugs, is being successfully used in the treatment of HCV infection. This combination has gained significant importance in the treatment of HCV infection due to reasons such as its low adverse event profile, easy tolerability by patients, high response rates at the end of treatment, low rates of treatment failure, not requiring dose adjustments in patients with advanced kidney failure or those on hemodialysis programs, and its effectiveness across all genotypes.[7]

Each HCV genotype has varying degrees of response to interferons. Similarly, it has been found that the progression to cirrhosis and the development of HCC occur more rapidly in certain HCV genotypes.[8] The increase in pan-genotypic treatment options and the elimination of the need for genotyping may lead to a decrease in the epidemiological data we currently have on genotypes in the future.[9] It is believed that this situation may lead to a decrease in epidemiological data regarding the genotypes of HCV infection in the future.

The most prevalent HCV genotype today is genotype 1, accounting for 46.2%, mainly due to its high prevalence in East Asia. At a rate of 30.1%, genotype 3 follows genotype 1. Genotype 4 instances are the most prevalent in the Middle East and North Africa.[10] According to research done in our nation, genotype 1b is the most commonly found genotype.[5,11] In our study, it was determined that the most frequently encountered genotype is genotype 1b, with a prevalence of 47.7%. The distribution of other genotypes has also been found to be consistent with the country data.

Many studies have been conducted to test the effectiveness of GLE/PIB treatment. In the studies, an extremely high SVR12 rate has been obtained, and it has been emphasized that GLE/PIB treatment is an effective treatment option.[12–14] A study involving 1,174 patients in Italy investigated the efficacy of GLE/PIB treatment in individuals with genotypes 1–4 HCV infection. In the study, an SVR12 yield of 98.8% was achieved.[15] In our study, a 100% rate of SVR12 was observed in the patients, while the rate of EVR was 81.8%. High rates of virological responses are indicative of the effectiveness of the GLE/PIB combination in treating CHC.

Following advancements in the pharmaceutical industry and biotechnology, the average human lifespan has increased. There are publications in studies examining the relationship between age and the virological response obtained after GLE/PIB treatment, indicating that the virological response that occurs after GLE/PIB treatment is not influenced by the patients' ages.[16,17] The reason for this may be the achievement of very high SVR12 values with GLE/PIB treatment. In our study, a threshold value of 65 years was determined to create a more homogeneous distribution, considering the average life expectancy data of our country. The rates of EVR were found to be 85% in the group aged 65 and over, while in the group under 65, it was 79.1%. When comparing the EVR rates of these two groups, no significant difference was found.

When examining publications that evaluate the relationship between viral load and the virological response achieved in CHC treatment, studies indicate that patients with lower HCV-RNA levels have higher rates of SVR and that the rate of treatment failure increases with higher viral loads.[18,19] Our study's comparisons based on HCV-RNA levels revealed no discernible correlation between HCV-RNA levels and EVR rates. There is a need for more comprehensive studies regarding the potential effects of viral load on the virological response.

The liver is an organ with a unique capacity for regeneration. However, in viral hepatitis, the liver loses its regeneration capacity due to fibrosis and enters a process of liver decompensation. When the balance between regeneration and fibrosis is disrupted, the levels of liver enzymes in the blood increase due to tissue destruction.[20] In a study aimed at demonstrating the normalization of ALT and AST after GLE/PIB treatment. In comparison to the initial ALT and AST levels, it was found that the levels measured at the end of treatment and the 4th week of treatment were much lower.[19] In our study, a decrease in patients' ALT and AST levels was observed as a result of the treatment. The results showed similar normalization of ALT and AST levels with GLE/PIB treatment.

Since GLE/PIB is primarily a combination eliminated through bile and feces, nephrotoxicity is not commonly observed. In a study examining the effects of sofosbuvir/ledipasvir and GLE/PIB treatments on serum creatinine, it was concluded that both sofosbuvir/ledipasvir and GLE/PIB treatments may increase serum creatinine levels to a low extent.[21] In our study, the median creatinine value at the end of treatment was discovered to be considerably more than the median creatinine value before treatment. In light of all this data, it should be kept in mind that while GLE/PIB treatment can be safely used in patients with CHC, it may slightly increase creatinine levels.

The adverse events arising from the development of DAAs have significantly decreased in both frequency and severity. In studies examining the adverse events in patients receiving GLE/PIB treatment, the most commonly observed adverse events were found to be headache, nausea, fatigue, and itching. Cases where ALT levels have risen have been reported rarely.[22,23] The patient's adherence to treatment in our study was at an excellent level. No patients discontinued treatment due to adverse effects. In the 4th week of treatment, adverse events were observed in 12 out of 44 patients (27.3%). By the end of treatment, the number of patients reporting adverse events decreased to 9 (20.5%). In line with studies in the literature, the two adverse effects most frequently noted were itching and fatigue. Nonetheless, one of the frequent adverse reactions documented in the literature, headache complaints, was not observed in the patients in our research.

CONCLUSION

Patients included in our study were treated effectively and reliably with the GLE/PIB combination. For every patient, SVR12 was obtained, and no non-response or relapses were observed in any of the patients. In comparisons made according to patients' treatment experiences, genotypes, and comorbidities, the EVR rates have also been found to be very high. There is a need for more comprehensive studies to determine whether the duration of GLE/PIB treatment in patients with CHC may be shorter in certain special patient groups.

Ethics Committee Approval: The Erciyes University Ethics Committee granted approval for this study (date: 23.07.2021, number: 2021/459).

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

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

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Not declared.

Author Contributions: Concept – KK, BA, OY, HNK, ZT, GKU, AYK; Design – KK, BA, OY, HNK, ZT, GKU, AYK; Supervision – KK, BA, OY, HNK, ZT, GKU, AYK; Resource – KK, BA, HNK, AYK; Materials – KK, BA; Data Collection and/or Processing – KK, BA; Analysis and/or Interpretation – KK, BA, HNK, ZT, GKU, OY, AYK; Literature Search – KK, BA, OY; Writing – KK, AYK; Critical Reviews – KK, BA, OY, HNK, ZT, GKU, AYK.

Peer-review: Externally peer-reviewed.

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Appendix 1. Analysis of changes in biochemical parameters of patients according to genotypes

	Before the treatment	4th week of treatment	8th week of treatment	4th week of follow-up	8th week of follow-up	p	Difference
Genotype 1a (n=8)							
ALT, IU/l	34 (20–104)[1]	13 (7–20)[2]	11 (6–21)[2]	13 (6–16)[2]	10 (6–16)[2]	**0.01**	**1>2**
AST, IU /l	33 (20–48)[1]	19 (13–25)[2]	13 (7–20)[2]	19 (13–25)[2]	19 (12–28)[2]	**0.01**	**1>2**
Platelet, 10^3/µl	230 (147–298)	212 (191–324)	217 (146–320)	267 (141–329)	246 (187–313)	0.13	–
Genotype 1b (n=21)							
ALT, IU /l	30 (8–254)[1]	12 (7–26)[2]	13 (5–32)[2]	12 (5–23)[2]	11 (7–20)[2]	**0.01**	**1>2**
AST, IU /l	33 (10–105)[1]	16 (8–25)[2]	16 (5–30)[2]	17 (6–25)[2]	17 (7–24)[2]	**0.01**	**1>2**
Platelet, 10^3/µl	235 (97–401)	213 (126–400)	214 (104–430)	219 (91–407)	226 (154–403)	0.57	–
Genotype 2 (n=7)							
ALT, IU /l	20 (11–114)[1]	12 (10–20)[2]	15 (11–23)[2]	14 (10–22)[2]	14 (10–29)[2]	**0.01**	**1>2**
AST, IU /l	25 (21–52)[1]	18 (14–25)[2]	18 (17–25)[2]	20 (14–26)[2]	19 (17–25)[2]	**0.01**	**1>2**
Platelet, 10^3/µl	219 (187–287)	232 (186–338)	224 (182–294)	235 (213–289)	268 (210–330)	0.43	–
Genotype 4 (n=6)							
ALT, IU /l	32 (5–114)[1]	12 (3–42)[2]	13 (7–23)[2]	14 (7–16)[2]	12 (5–14)[2]	**0.01**	**1>2**
AST, IU /l	23 (15–87)[1]	15 (12–29)[2]	18 (13–22)[2]	16 (10–31)[2]	17 (9–28)[2]	**0.01**	**1>2**
Platelet, 10^3/µl	208 (179–315)	229 (157–283)	210 (148–304)	197 (172–331)	204 (150–322)	0.54	–
Total (n=44)							
ALT, IU /l	34 (5–254)[1]	13(3–56)[2]	15 (4–32)[2]	14 (5–23)[2]	13 (5–29)[2]	**0.01**	**1>2**
AST, IU /l	32 (10–158)[1]	18 (8–38)[2]	18 (5–30)[2]	20 (8–38)[2]	18 (7–28)[2]	**0.01**	**1>2**
Platelet, 10^3/µl	220 (97–401)	218 (126–400)	217 (104–430)	235 (91–407)	238 (140–403)	0.34	–
Creatinine, mg/dl	0.72 (0.49–1.11)[1]		0.79 (0.5–1.23)[2]		0.8 (0.53–1.1)[2]	**0.01**	**2>1**

All data are given as median (min–max). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase. Data related to genotype 3 are not statistically significant because there were only 2 patients infected with genotype 3. Therefore, genotype 3 data are not included separately in the table.