Research Article

95

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Clinical Efficacy and Safety of Direct-Acting Antivirals in Chronic Hepatitis C Treatment: Real-World Data

Kronik Hepatit C Tedavisinde Doğrudan Etkili Antivirallerin Klinik Etkinliği ve Güvenliği: Gerçek Yaşam Verileri

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ABSTRACT

Objectives: Chronic hepatitis C (CHC) disease is an important health problem that affects approximately one hundred and seventy million people worldwide and can cause cirrhosis and liver cancer. In this study, the efficacy and side effects of new generation direct acting antivirals (DAA) agent on the hepatitis C infection profile were evaluated.

Materials and Methods: This retrospective observational study included 210 eligible CHC patients treated with DAAs. They received sofosbuvir ± ledipasvir ± ribavirin, paritaprevir/ritonavir/ombitasvir/dasabuvir ± ribavirin and glecaprevir/pibrentasvir (GLE/PIB). A hepatitis C virus-RNA level of ≤15 IU/mL at 12 or 24 weeks after the end of treatment was considered a sustained virological response (SVR). The side-effect profile and SVR were recorded, and the data were analyzed.

Results: SVR12 was evaluated in 154 patients, and the rate of SVR was found to be 98% (152/154). At the 24th week after treatment, data of 153 patients were available, and SVR was achieved at a rate of 99% (152/153). During treatment, fatigue and itching were common adverse effects. One patient failed to complete treatment during the treatment period due to adverse effects. The patient receiving GLE/PIB developed and progressively worsened allergic rashes. The treatment could be administered only for 3 weeks, and the treatment was terminated on the basis of the lack of tolerability.

Conclusion: In our study, we concluded that the new generation DAA are highly effective with high SVR rates. It was also concluded that they are safe because of their low and tolerable side-effect profile.

Keywords: Chronic hepatitis C, direct-acting antiviral agents, sustained virologic response, adverse events

ÖZ

Amaç: Kronik hepatit C (KHC) hastalığı, tüm dünyada yaklaşık yüz yetmiş milyon insanı etkileyen ve siroz ve karaciğer kanserine neden olabilen önemli bir sağlık sorunudur. Çalışmada, yeni nesil doğrudan etkili antiviral (DEA) ajanların KHC virüsünün enfeksiyon profilinin tedavisinde etkinliği ve yan etkileri değerlendirilmiştir.

Gereç ve Yöntemler: Retrospektif gözlemsel bir çalışma olarak planlanan bu çalışmaya DEA'larla tedavi edilen 210 uygun KHC hastası dahil edildi. Sofosbuvir ± ledipasvir ± ribavirin, paritaprevir/ritonavir/ombitasvir ± dasabuvir ± ribavirin ve glecaprevir/pibrentasvir (GLE/PIB) tedavileri verildi. Tedavinin bitiminden 12 veya 24 hafta sonra ≤15 IU/mL'lik bir hepatit C virüs-RNA seviyesi, kalıcı bir virolojik yanıt (KVY) olarak kabul edildi. Yan etki profili ve kalıcı virolojik yanıtlar kaydedildi ve veriler IBM SPSS 21 programı ile analiz edildi.

Bulgular: Tedavi bitiminden 12 hafta sonra KVY oranı 154 hastada hesaplandı ve %98 olarak saptandı (152/154). Tedavi sonrası 24. haftada 153 hastanın verileri mevcuttu ve KVY %99 (152/153) olarak analiz edildi. Yorgunluk ve kaşıntı tedavi sürecinde yaygın görülen yan etkilerdi. Bir hastanın tedavisini yan etkiler nedeniyle tamamlayamadığı kaydedildi. GLE/PIB alan bu hastada gelişen alerjik döküntülerin giderek artması üzerine hastaya üç hafta boyunca tedavi verilebildi.

Sonuç: Çalışmamızda yeni nesil DEA'ların yüksek KVY oranları ile oldukça etkili olduğu sonucuna varılmıştır. Ayrıca, düşük ve tolere edilebilir yan etki profili gösterdikleri için güvenli olarak değerlendirilmiştir.

Anahtar Kelimeler: Kronik hepatit C, direkt etkili antiviral ajanlar, kalıcı virolojik yanıt, yan etkiler

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Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver diseases worldwide (1). Up to 85% of HCV-infected patients cannot achieve virus clearance and develop chronic infection. Because of chronic infection, liver fibrosis, cirrhosis, extrahepatic involvement, and hepatocellular carcinoma (HCC) may develop in patients (2).

Epidemiological studies in Turkey have shown that chronic hepatitis C (CHC) infection occurs in approximately 1% of the Turkish population, with genotype 1 being the common genotype (92.1%), followed by genotypes 2, 3, and 4 (3). Direct-acting antiviral (DAA) drugs used in the treatment of HCV inhibit the NS3/4A, NS5A, and NS5B regions in the virus genome by stopping the replication of the virus (4).

In our study, we aimed to evaluate the effectiveness and safety of DAA agents available in our country for treating chronic HCV infection in a heterogeneous group of patients.

Materials and Methods

The study was approved by the Ethics Committee for Clinical Research at the Eskişehir Osmangazi University, conforming to the protocols in accordance with the Declaration of Helsinki (approval number: 18/2020).

This retrospective observational study included 172 patients who received DAA treatment with CHC diagnosis in a university hospital infectious diseases and clinical microbiology outpatient clinic between July 2016 and December 2019 and whose persistent virological response level could be assessed after treatment. The distribution of patients is summarized in Figure 1.

The treatment and post-treatment responses of the patients were recorded in the outpatient clinic patient files and the hospital information management system.

Data were collected during treatment and 12 and 24 weeks after treatment. Demographic, clinical, and laboratory parameters (blood count, creatinine, liver panel, prothrombin time/international normalized ratio, viral serology, HCV-RNA level and genotype, liver biopsy findings, radiologic findings, previous treatment) were recorded for all patients. Data on tolerability and safety analyses, adverse events (AE), and drug discontinuation rates owing to AEs were recorded.

Virological response rates were analyzed according to the HCV-RNA levels of the patients. The presence of HCV-RNA was studied by nucleic acid extraction and quantitative real-time polymerase chain reaction (PCR) (artus hepatitis C QS-RGQ, Qiagen). The detection limit of the test used was 15 IU/mL. Genotype determination was performed using real-time PCR using the Bosphore HCV Genotyping Kit V3 and the Montania 4896 device (Anatolia Diagnosis and Biotechnology products, Turkey). In this method, the required HCV-RNA level to detect the HCV genotype is >100 IU/mL. All tests were performed according to the manufacturer's instructions.

Histopathological diagnosis using the liver modified histological activity index (HAI) and ISHAK scoring systems was performed. Those with fibrosis stage F0-3 according to the ISHAK score were non-cirrhotic and those with F4-6 were considered cirrhotics. The decision regarding the agent used in the treatment, its duration, and dose has been made by considering the Communique on Health Practices in our country, both national and international.

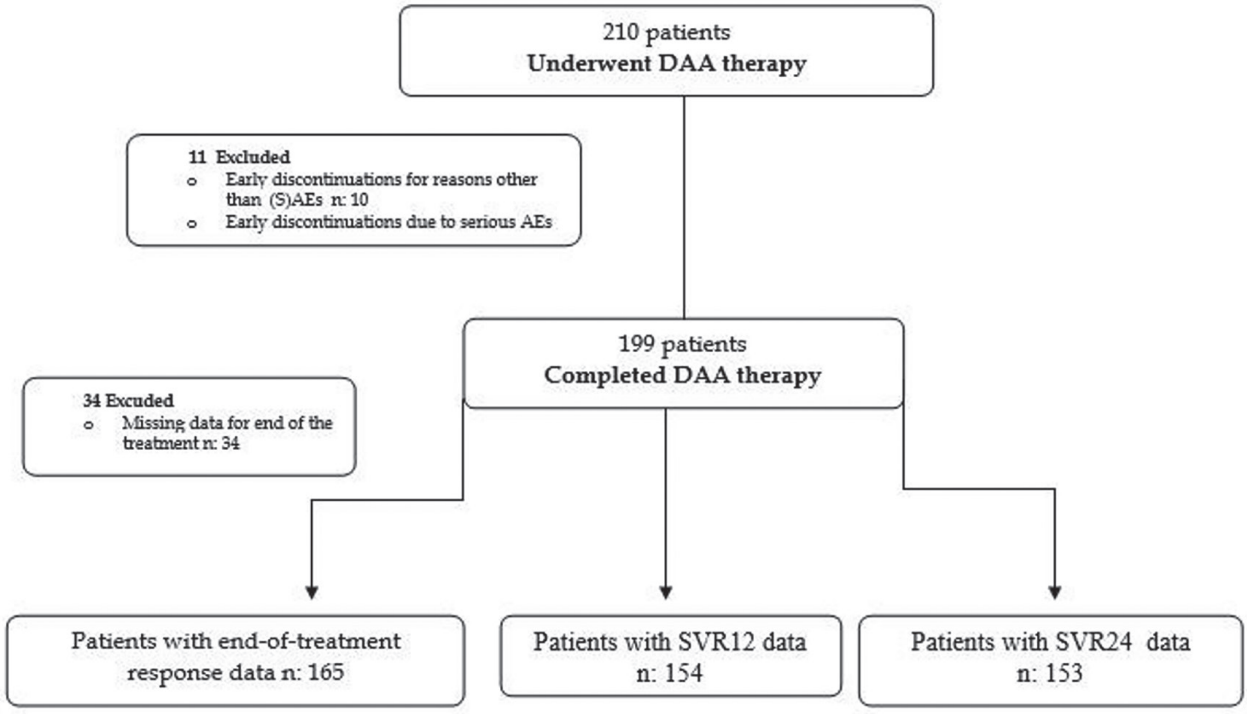

Figure 1. Flowchart showing the distribution of the study populations

DAA: Direct acting antivirals, SVR12: Sustained virological response 12 weeks after treatment, SVR24: Sustained virological response 24 weeks after treatment

Statistical Analysis

Data analysis was performed using IBM Statistical Package for Social Sciences version 21.0. Summary values of quantitative variables are shown as mean ± standard deviation or median (Q1-Q3), summary values of qualitative variables are shown as frequency and percentage. The conformity of quantitative variables to normal distribution was investigated using the Shapiro-Wilk test. Comparison of two independent groups was performed using the Mann-Whitney U test because normal distribution was not found. The relationship between qualitative variables was evaluated using chi-square analysis. The cases obtained with a p-value <0.05 because of the analysis were considered significant.

Results

Patient Characteristics

The clinical and demographic characteristics of the patients are presented in Table 1. The patients included in the study were 49.4% male (n=85) and 50.6% (n=87) female (Table 1). The mean age of all patients was 56.39±15.47 15.47 years (18-81). The mean duration of diagnosis of CHC was 5.4±5.93 (0.5-30) years. Of the patients, 69.8% (n=120) were naive, and 30.2% (n=52) had previously received interferon-based treatment. The most common genotype in the HCV genotype distribution of patients was genotype 1 (1a+1b) in 84.9%, followed by genotypes 3, 2 and 4, respectively. At the beginning of treatment, most patients were non-cirrhotic (84.9% non-cirrhotic, 15.1% cirrhotic). All cirrhotic patients had compensated cirrhosis, and there was no patient with decompensated cirrhosis.

The most common chronic disease in the patients was hypertension at a rate of 40% (n=70), diabetes mellitus 22% (n=38) and asthma 15.6% (n=27) were other common comorbid diseases. There was one human immunodeficiency virus-positive patient with coinfection, and there was no patient with hepatitis B virus infection.

Table 1. Demographic and clinical characteristics of patients

	n (%)
Sex	
Male	85 (49.4)
Female	87 (50.6)
Age	
18-64	112 (65.1)
≥65	60 (34.9)
Genotype	
1a	21 (12.2)
1b	125 (72.7)
2	4 (2.3)
3	20 (11.6)
4	2 (1.2)
Treatment experience	
Naive	120 (69.8)
Experienced	52 (30.2)
Fibrosis stage	
Non-cirrhotic	146 (84.9)
Cirrhotics	26 (15.1)
Total	**172 (100)**

At the beginning of the treatment, the mean alanine transaminase (ALT), aspartate tranaminase (AST), and HCV-RNA levels were 50±43 U/L, 41±24 U/L, and 3139571±5314478 IU/mL, respectively. Liver biopsy results were available in 85.5% (n=147) of the patients before treatment. The mean HAI and fibrosis stage were 6.9±2.1 (3-15) and 2.5±1.3 (0-6), respectively. The mean alpha-fetoprotein (AFP) level studied at the beginning of treatment in the cirrhotic patient group (9.65±16.50 µg/L) was found to be statistically significantly higher than the mean (4.11±3.99) in the non-cirrhotic patient group (p=0.001).

Patients were given 3 separate regimens according to the current treatment options of the study period: the sofosbuvir (SOF)-containing regimen, the paritaprevir/ritonavir/ombitasvir (PRO)-containing regimen, and glecaprevir/pibrentasvir (GLE/PIB) therapy. In some patients receiving SOF- and PRO-based regimens, ribavirin (RBV) treatment was added according to genotype. Of the patients included in our study had different treatment regimen groups; 94 (55.2%) received paritaprevir/ritonavir/ombitasvir ± dasabuvir ± RBV, 62 (36%) received SOF/LDV ± RBV, 15 (8.8%) received GLE/PIB, and 1 received PRO + RBV.

Treatment Efficacy and Sustained Virological Response

In our study, the rate of achieving SVR12 was 98% (152/154), and the rate of achieving SVR24 was 99% (153/154) (Table 2).

The rate of patients achieving SVR12 was analyzed according to gender, genotype, treatment regimen, previous treatment status, level of liver damage, and age (Table 3). In terms of reaching SVR12, no statistically significant difference was found in the other groups except for the genotype (Figure 2, 3).

Statistically significant difference between genotypic groups; groups are not homogeneous, the number of patients with genotype 2 and genotype 3 is less than the number of patients with other genotypes; in addition, it was thought that it may be related to the relapse cases seen in these groups.

Safety

Adverse effects were observed during treatment in 49 (28.5%) of 172 patients included in the study. Some patients had more than one side effect. There was 1 patient whose treatment was terminated because of serious side effects and whose treatment could not be completed. The patient who developed pruritus and rash from the first dose of GLE/PIB treatment, which gradually increased, and whose treatment was interrupted because the

Table 2. Overall treatment outcome

	Virological response n (%)
End of the treatment	162/165 (98%)
SVR12	152/154 (98%)
SVR24	152/153 (99%)

SVR12: Sustained virological response 12 weeks after treatment, SVR24: Sustained virological response 24 weeks after treatment

Table 3. The rate of achieving SVR12 and p-values according to the descriptive characteristics of the patients

	SVR12 (+), (n, %)	SVR (-), (n, %)	p
Sex			
Male	71 (97.3%)	2 (2.7%)	0.223
Female	81 (100%)	0	
Age			
18-64	98 (98%)	2 (2%)	0.542
≥65	54 (100%)	0	
Fibrosis stage			
Non-cirrhotic	130 (99.2%)	1 (0.8%)	0.277
Cirrhotics	22 (95.7%)	1 (4.3%)	
Treatment experience			
Experienced	45 (95.7%)	2 (4.3%)	0.092
Naive	107 (100%)	0	
Genotype			
1a	20 (100%)	0	**0.040**
1b	111 (100%)	0	
2	3 (75%)	1 (25%)	
3	16 (94.1%)	1 (5.9%)	
4	2 (100%)	0	
Therapeutic regimen			
SOF/LDV ± RBV	53 (96.4%)	2 (3.6%)	0.288
PRO ± DSV ± RBV	86 (100%)	0	
GLE/PIB	13 (100%)	0	

SVR: Sustained virological response, SVR12: Sustained virological response 12 weeks after the treatment, SOF/LDV ± RBV: Sofosbuvir/ledipasvir ± ribavirin, PRO ± DSV ± RBV: Paritaprevir/ritonavir/ombitasvir ± dasabuvir ± ribavirin, GLE/PIB: Glecaprevir/pibrentasvir

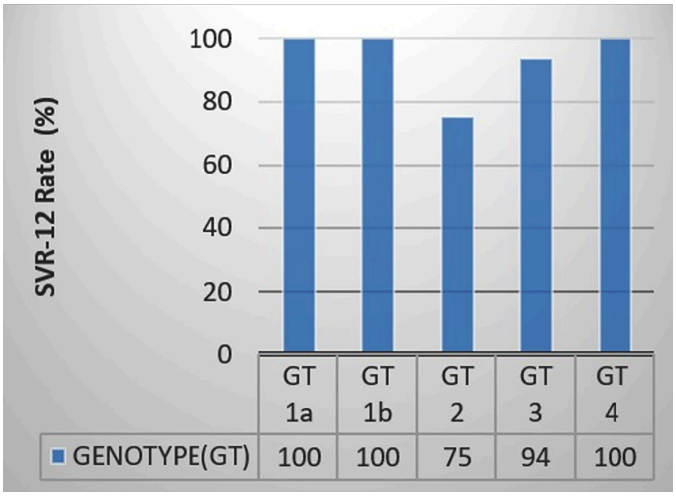

Figure 2. Sustained virologic response 12 rates of different genotypes (p=0.040)

SVR12: Sustained virological response 12 weeks after treatment

condition became intolerable in the 3rd week of treatment was excluded from the study. The most common side effects observed during the treatment process in all patients were itching (11%), weakness (9.3%), and stomach pain (6.4%). Of the 49 patients with side effects, 31 (63.3%) received the PRO-containing regimen, 17 (34.7%) received the SOF-containing regimen, and 1 (2%) received the GLE/PIB-containing regimen. Itching complaints were more common in the PRO regimen, and 15 of 19 patients received the PRO-containing regimen and 4 received the SOF-containing regimen.

Discussion

HCV infection is one of the main causes of chronic liver diseases worldwide. As a result of chronic infection, liver fibrosis, cirrhosis, extrahepatic involvement, and HCC can develop in patients (2). The primary aim of treatment for chronic HCV infection is the prevention of hepatic and extrahepatic complications such as liver necroinflammation, fibrosis, cirrhosis, HCC, and ultimately death by eradicating the HCV. The aim of treatment includes normalization of serum aminotransferases, undetectable HCV-RNA in serum, and improvement of histological findings in the liver.

In many clinical studies evaluating treatment response in patients treated with DAA, mean SVR of over 90% has been demonstrated (5,6). In a multicenter meta-analysis conducted by Perazzo et al. (8), it was found that DAA agents are highly effective. In this study, which included real-life data and more than 57,000 patients, the overall mean of patients with a sustained virological response was 98%. This rate was similar to rates reported in many other observational cohort studies worldwide involving large, real-life data with DAA agents (7-10). In our study, the rate of SVR12 was 98% and that of SVR24 was 99%, similar to other studies in patients who received DAA agents.

In a multicenter study conducted in our country (n=862), they found the rate of SVR12 to be 99.5% in the non-cirrhotic patient group and 95.5% in the cirrhotic patient group. A comparison was made between these two groups according to the cirrhosis status, and they found a statistically significant difference between the groups in terms of response in SVR12 (p<0.016) (11). In our study, the rate of SVR12 was found to be 99% in the non-cirrhotic patient group and 95% in the cirrhotic patient group, and it was found to be lower in cirrhotic patients, similar to other studies.

There are also studies that evaluate the treatment response according to the treatment experience status. In a study conducted by Mizokami et al. (12) in 2021, the rate of SVR12 was determined to be 97.55% in patients with treatment experience and 99.05% in the treatment naive patient group, and it was shown that there was no significant difference between the groups in terms of reaching SVR12. In our study, there was no statistically significant difference in terms of access to SVR between the groups in terms of treatment experience (p=0.092).

In our study, the SVR ratios according to the genotypes of the patients were examined. The response rate was 100% in patients with genotypes 1 and 4, 75% in patients with genotype 2, and 94% in patients with genotype 3. There was a significant difference between genotypic groups in terms of reaching SVR12 (p=0.040).

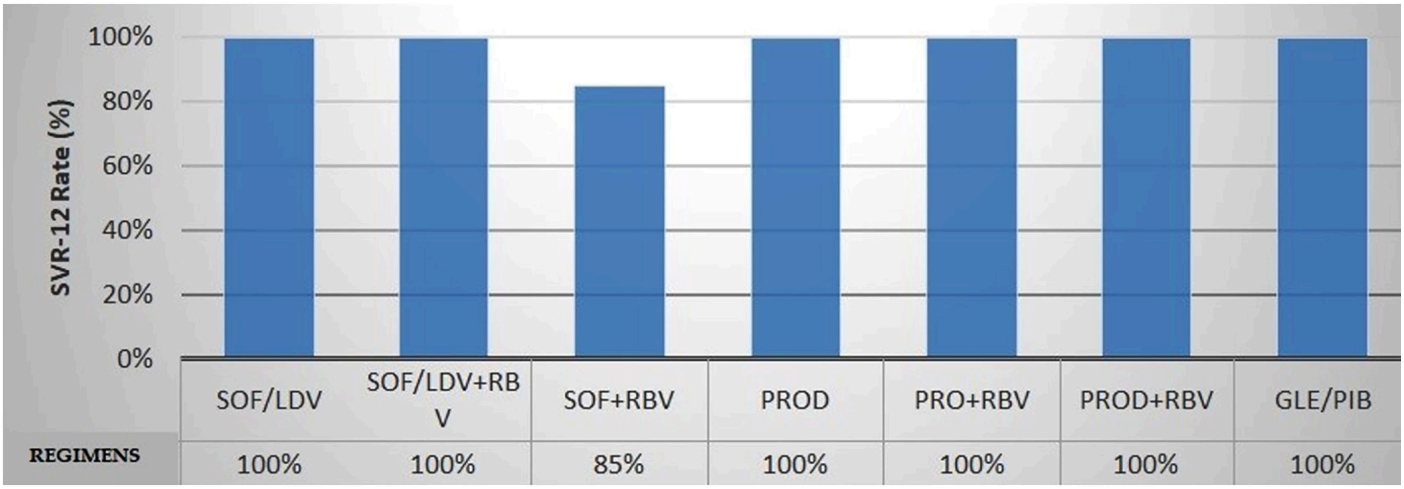

Figure 3. Sustained virologic response 12 rates of each direct-acting antiviral regimen (p=0.288).

SVR12: Sustained virological response 12 weeks after treatment, SOF: Sofosbuvir, LDV: Ledipasvir, RBV: Ribavirin, PROD: Paritaprevir/ritonavir/ombitasvir ± dasabuvir, GLE/PIB: Glecaprevir/pibrentasvir

The reason for the significant difference may be that the distribution of the number of patients among the genotypic groups is not homogeneous. Similar to Turkey, most of the patients in our study were patients with genotype 1 infection. It was thought that this condition developed because of the small number of patients with genotypes 2 and 3 infections and the occurrence of recurrence cases in these groups.

In a retrospective study of 219 patients by Khan et al. (13), it was found that AST and ALT levels were significantly reduced with treatment and reached normal levels in patients who were administered DAAs. In our study, a statistically significant decrease in ALT, AST, and HCV-RNA values during treatment was detected (p<0.001). At the same time, the decrease in gamma-glutamyl transpeptidase and AFP parameters at the end of treatment was statistically significant compared with the start of treatment (p<0.001; p=0.028, respectively). Data on the effect of these biochemical changes on treatment success have not been determined.

In our study, treatments were generally well tolerated and the side effects that developed were mild. The most common side effects were itching (11%), weakness (9.3%), and stomach pain (6.4%). There was one patient whose treatment was interrupted because of intolerance of treatment; the patient who received GLE/PIB treatment did not complete the treatment process because of the increasing rash in the 3rd week of treatment. In the literature, it has been reported that the rate of side effects increases when RBV is added to the treatment. In meta-analyses evaluating SOF/LDV ± RBV treatments, the rate of side effects was higher in groups with RBV; weakness, fatigue, nausea, insomnia, and anemia are reported to be more common (14,15). In our study, 51 patients (29.7%) were receiving RBV-containing DAA treatment, and side effects were similarly more frequent in these patients. Four of the patients already had anemia at the beginning of treatment. However, 17 of the 46 patients (36%) without anemia at the beginning of treatment had anemia at the end of treatment.

In our study, adherence to treatment was quite high in all patients. The SVR rate was as high as 98% in all patients receiving DEA treatment. There was no difference in virological response between the different DAA treatment regimens. There was a significant difference between genotypic groups in terms of SVR. The reason for this difference was thought to be the difference in distribution between the groups and the effect of relapse cases in genotypic groups with a low number of patients. It was found that the cirrhosis status or past treatment experience of the patients did not differ in terms of SVR access.

Study Limitations

Our study was planned retrospectively; therefore, the laboratory and clinical data about the patients were not complete, and the characteristics of the patients and the number of patients in the treatment groups were not evenly distributed as limited aspects of our study.

Conclusion

DEA treatments were evaluated as highly effective and safe because of the low and tolerable side effects.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee for Clinical Research at the Eskişehir Osmangazi University, conforming to the protocols in accordance with the Declaration of Helsinki (approval number: 18/2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.D., E.D.K., Concept: A.D., E.D.K., Design: A.D., E.D.K., Data Collection or Processing: A.D.,

S.N.A., Analysis or Interpretation: A.D., Literature Search: A.D., E.D.K., S.N.A., Writing: A.D.

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