RESEARCH ARTICLE / ARAŞTIRMA

DOI: 10.4274/mjima.galenos.2023.23061
Mediterr J Infect Microb Antimicrob 2023;12:23061
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2023.23061

The Outcomes of Direct-acting Antiviral Treatment in 177 Patients with Hepatitis C Virus: A Single-center Experience

Hepatit C Virüs Enfeksiyonu Olan 177 Hastada Doğrudan Etkili Antiviraller ile Tedavinin Sonuçları: Tek Merkez Deneyimi

Ayşin KILINÇ TOKER, Ayşe TURUNÇ ÖZDEMİR, Esma ERYILMAZ EREN, Duygu ÇERÇİOĞLU ÖZDEMİR, Deniz KALAMAK GÜZEL, Tuğba TOK, Zehra BEŞTEPE DURSUN, Musa GÖKSU, İlhami ÇELİK

Kayseri City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Kayseri, Turkey

Abstract

Introduction: Hepatitis C virus (HCV) is an essential cause of hepatitis, cirrhosis, and hepatocellular carcinoma. Hepatitis C virus is a global public health problem. "Field practice" in patients with HCV infection is significant for directly observing treatment responses with antiviral agents. Our study aimed to evaluate the effectiveness of direct-acting antivirals (DAAs) in Kayseri City Hospital.

Materials and Methods: Our retrospective observational study, conducted at a single center, evaluated HCV-RNA-positive patients who were genotyped between January 2019 and April 2023. Demographic characteristics, laboratory values, treatment agents, and HCV genotypes of the patients were recorded using the hospital information system. The primary endpoint of the study was the sustained virological response 12 weeks after treatment.

Results: In our five-year study involving 177 patients, the average age was 60.6, and 55.4% (n=98) of the participants were male. Genotype 1b was the most common at 51.8%, followed by genotype 4 at 19.2%. Additionally, six of 11 Syrian patients were identified as genotype 3. The glecaprevir/pibrentasvir combination was administered to 91.5% of the patients, while the sofosbuvir/velpatasvir/voxilaprevir combination was started in 8.5% (n=15). A total of 6.2% of the patients had prior treatment experience. At week 12, all patients exhibited negative HCV-RNA levels, resulting in a 100% treatment success rate.

Conclusion: These two DAAs currently used in HCV infection were highly effective. The prevalence of genotype 4 in our region was higher than the national HCV genotype distribution.

Keywords: Direct-acting antivirals, sustained viral response, hepatitis C

Öz

Giriş: Hepatit C virüsü (HCV), hepatit, siroz ve hepatosellüler karsinomun önemli bir nedenidir ve global bir halk sağlığı sorunudur. Hepatit C virüs enfeksiyonu olan hastalarında "saha pratiği", antiviral ajanlarla tedavi yanıtlarının doğrudan görülmesi açısından çok önemlidir. Çalışmamızda Kayseri Şehir Hastanesi'nde doğrudan etkili antivirallerin (DAA'lar) etkinliğini değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: Tek merkezli retrospektif gözlemsel olan çalışmamız Ocak 2019-Nisan 2023 tarihleri arasında HCV RNA'sı pozitif, genotiplendirmesi yapılmış hastalar değerlendirmeye alındı. Hastaların demografik özellikleri, laboratuvar değerleri, tedavi ajanları ve HCV genotipleri hastane bilgi sistemi aracılığıyla kaydedildi. Birincil sonlanım noktası tedaviden 12 hafta sonra kalıcı virolojik yanıt olarak kabul edildi.

Bulgular: Yüz yetmiş yedi hasta ve beş yıllık dönemi kapsayan çalışmamızda yaş ortalaması 60,6 ve hastaların %55,4'ü (n=98) erkekti. En sık genotip 1b (%51,8) idi ve ikinci sırada %19,2 ile genotip 4 vardı. Ek olarak Suriyeli 11 hastanın altısı genotip 3'tü. Hastaların %91,5'ine Glecaprevir/pibrentasvir kombinasyonu başlanmıştı, %8,5'ine ise (n=15) sofosbuvir/velpatasvir/voxilaprevir kombinasyonu başlandı. Hastaların %6,2'si tedavi deneyimli idi. Tüm hastaların 12. haftadaki kontrol HCV-RNA düzeyleri negatif ve tedavi başarı oranı %100'dü.

Cite this article as: Kılınç Toker A, Turunç Özdemir A, Eryılmaz Eren E, Çerçioğlu Özdemir D, Kalamak Güzel D, Tok T, Beştepe Dursun Z, Göksu M, Çelik İ. The Outcomes of Direct-acting Antiviral Treatment in 177 Patients with Hepatitis C Virus: A Single-center Experience. Mediterr J Infect Microb Antimicrob. 2023;12:23061.

Address for Correspondence/Yazışma Adresi: Ayşin KILINÇ TOKER MD, Kayseri City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Kayseri, Turkey
Phone: +90 352 315 77 00 **E-mail:** dr.aysin@gmail.com **ORCID ID:** orcid.org/0000-0002-6775-1234
Received/Geliş Tarihi: 26.10.2023 **Accepted/Kabul Tarihi:** 07.12.2023

Published: 07.12.2023

Sonuç: Hepatit C enfeksiyonunda güncel olarak kullanılan bu iki DAA' lar yüksek etkinliğe sahipti. Bölgemizdeki genotip 4'ün yaygınlığı ulusal HCV genotip dağılımından daha yüksekti.
Anahtar Kelimeler: Doğrudan etkili antiviraller, sürekli viral yanıt, hepatit C

Introduction

Hepatitis C virus (HCV) is a significant health problem worldwide. It is one of the most important causes of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma[1]. Worldwide, an estimated 58 million people have chronic HCV infections, and about 1.5 million new infections occur each year. An anticipated 3.2 million adolescents and children are affected by chronic HCV infection-HCV can lead to both acute and chronic conditions. Acute HCV infections are generally asymptomatic, and most do not cause life-threatening illness. In about 30% (15-45%) of the infected individuals, the virus clears spontaneously within six months of infection without treatment. The remaining 70% (55-85%) develop chronic HCV infection. The risk of cirrhosis in those with chronic HCV infection ranges from 15% to 30% within 20 years [2].

HCV, like many other RNA viruses, has genetic diversity. The high replication rate of HCV and the absence of the error repair function of the RNA-dependent RNA polymerase enzyme are associated with genetic diversity. In this way, HCV can escape the immune response and antiviral treatment. HCV has been shown to have eight major genotypes and around 80 subtypes[3]. According to studies examining HCV genotype distributions in our country, in approximately 70-90%, genotype 1 appears to be the most dominant[1,4,5].

The introduction of interferon-free direct antiviral agent (DAA) therapies has reinvented the treatment landscape for HCV. After 2015, oral combination DAAs became the standard for treating HCV infection. Since then, they have presented several advantages, including a specific target of HCV viral replication (thus appearing less dependent on host characteristics) and very high sustained virological response rates with fewer side effects and lower pill load. Based on these foundations, the World Health Organization has published an ambitious target to eradicate HCV infection worldwide by 2030[1,6,7].

This study aims to demonstrate the treatment response of newly emerging direct-acting antivirals in HCV-infected patients.

Materials and Methods

This retrospective, observational study, conducted at a single center, was performed in the Clinic of Infectious Diseases and Clinical Microbiology, Kayseri City Hospital. The study was approved by the Kayseri City Hospital of Clinical Research Ethics Committee (decision no: 870, date: 11.07.2023). The patients were scanned from the files and the hospital information system, and those infected with HCV (anti-HCV-positive) were identified. All patients with HCV-RNA >15 IU/ml and receiving DAA treatment were included in the study. Out of 184 patients, seven were excluded from the study because they stopped following the treatment. HCV-RNA levels, age, gender, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, and "international normalized ratio" (INR) values were recorded at the initiation of treatment, the 4th week and the 12th week. The HCV-RNA level at the 12th week after therapy was used to evaluate the permanent viral response. Based on patients' treatment experiences, two groups were identified: naïve and treatment-experienced. Additionally, classifications were made according to nationality, distinguishing between Turkish and Syrian citizens. Genotype status was categorized into groups 1a, 1b, 2, 3, 4, and mixed.

Quantitative real-time (reverse transcriptase) polymerase chain reaction (PCR) determined HCV-RNA in plasma samples. Viral nucleic acid isolation was performed using "The QIAsymphony DSP virus/pathogen midi kit" (Qiagen, Germany) and the QIAsymphony SP/AS (Qiagen, Germany) instrument. Quantitative HCV-RNA PCR tests were performed on the Rotor-Gene Q real-time PCR instrument (Qiagen, Germany). HCV genotyping test was performed using the real-time PCR method with the Montania 4,896 (Anatolia Geneworks, Turkey) device and Bosphore HCV genotyping (Anatolia Geneworks, Turkey) kit.

Statistical Analysis

In the statistical evaluation of the data obtained from the study, categorical data were summarized as frequency and percentage, and continuous data as mean±standard deviation or median value (interquartile range, minimum-maximum) depending on the data distribution. The Shapiro-Wilk test was used to evaluate the normality of the data. Comparisons of non-normally distributed laboratory values over time were analyzed using the Friedman test. If statistical significance was found, pairwise comparisons were made using the Wilcoxon signed-rank test. The significance level was taken as 0.05.

Results

The mean age of the 177 patients in the five-year study was 60.6±14.5 years (minimum: 22, maximum: 82). Of the patients, 55.4% (n=98) were male. Citizenship distribution included 93.8% (n=166) Turkish citizens and 6.2% (n=11) Syrian citizens. The median baseline HCV-RNA level was 1,524x10^3 IU/ml.

Among the patients, four (2.3%) were genotype 1a, 97 (54.8%) were genotype 1b, 12 (6.8%) were genotype 2, 22 (12.4%) were genotype 3, 34 (19.2%) were genotype 4, and eight (4.5%) had mixed genotypes. Additionally, six (54.5%) out of 11 Syrian patients were genotype 3. Eleven (6.2%) of the patients had previous treatment experience. According to the treatment regimens used, glecaprevir/pibrentasvir was administered in 91.5% (n=162), and sofosbuvir/velpatasvir/voxilaprevir combination was administered in 8.5% (n=15). The basic characteristics of the patients are shown in Table 1.

When the patients' total bilirubin, AST, ALT, INR, platelet count, and alpha-fetoprotein (AFP) levels, baseline, fourth week, and twelfth-week values were examined, statistical significance was found over time in variables other than INR value and platelet count-(Friedman test, p=0.007 for bilirubin and other p values <0.001). The difference in time between the baseline value and the values at the 4th and 12th weeks was made with the Wilcoxon signed-row test. Total bilirubin levels increased significantly at four weeks (p=0.005), while AST, ALT, and AFP levels decreased significantly at four and 12 weeks compared to baseline values (Table 2). All patients had negative control HCV-RNA levels at week 12; the treatment success rate was 100%.

The distribution of HCV genotypes by years is shown in Graphic 1.

Discussion

In our five-year study involving 177 patients, the average age was 60.6, with 55.4% (n=98) of the participants being male. The most common genotype was 1b (51.8%), with six out of 11 Syrian patients having genotype 3. The glecaprevir/pibrentasvir combination was administered to 91.5% of the patients, and 6.2% had prior treatment experience. Control HCV-RNA levels of all patients at week 12 were negative, and the treatment success rate was 100%.

Table 1. Baseline characteristics of the 177 patients included in the study

Characteristics	n (%)
Mean age, standard deviation, (min-max); years	60.6±14.5 (22-82)
Male	98 (55.4)
Syrian	11 (6.2)
Median HCV-RNA level (min-max); (x10^3 IU/ml)	1,524 (0.053-72,720)
Treatment regimens	
Glecaprevir/pibrentasvir	162 (91.5)
Sofosbuvir/velpatasvir/voxilaprevir	15 (8.5)
HCV genotype	
HCV1a	4 (2.3)
HCV1b	97 (54.8)
HCV2	12 (6.8)
HCV3	22 (12.4)
HCV4	34 (19.2)
Mix*	8 (4.5)
Previous treatment (IFN-experienced)	11 (6.2)
Patients with normal bilirubin levels	163 (92.1)
Patients with normal AST values	77 (43.5)
Patients with normal ALT values	72 (40.7)
Patients with normal PLT values	132 (74.6)
Patients with normal INR values	78 (44.1)
Patients with normal AFP values	99 (55.9)

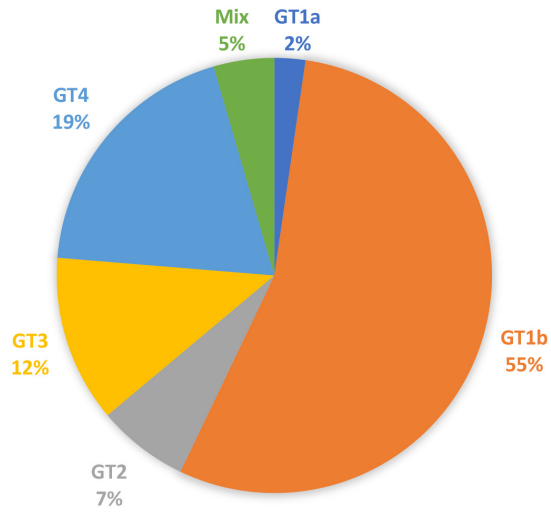
*Mix=1b-3, 2-3, 3-4, 3-4.

INR: International normalized ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, min-max: Minimum-maximum

Table 2. Change in the laboratory values of the patients

Baseline factors (n)	Admission, median (IQRs)	4th week, median (IQRs)	12th week, median (IQRs)	Friedman test p value	Wilcoxon analysis p value
Bilirubin (mg/dl)	0.6 (0.4-0.85)	0.6 (0.5-0.9)	0.5 (0.4-0.8)	0.007	a<b 0.005 a>c 0.891
AST (U/l)	34 (37-59)	19 (12-21)	19 (15-23)	<0.001	a>b<0.001 a>c <0.001
ALT (U/l)	38 (26-65)	16 (12-21)	14 (11-18)	<0.001	a>b<0.001 a>c<0.001
INR	1.04 (1-1.17)	1.06 (1-1.12)	1.05 (1-1.19)	0.059	
Platelets (10^3/mm^3)	217 (151-266)	220 (158-280)	223 (164-270)	0.063	
AFP (U/ml)	3.6 (2.4-7)	2.9 (2-5.6)	2.9 (2-4.8)	<0.001	a>b<0.014 a>c<0.001

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, Bilirubin: Total bilirubin, AFP: Alpha-fetoprotein, IQRs: Interquartile ranges, INR: International normalized ratio



Graphic 1. Distribution of HCV genotypes
HCV: Hepatitis C virus

At least seven major HCV genotypes have been identified worldwide, each containing multiple subtypes. In a new study reported from India in 2018, the number of genotypes increased to eight with the inclusion of a new genotype[8]. There are significant regional differences in the distribution of HCV genotypes. HCV genotype 1 is the most common worldwide, followed by genotypes 3, 4, and 2. While genotypes 1 and 3 are common worldwide, the most significant proportion of genotypes 4 and 5 are in low-income countries[9,10]. In studies conducted in our country, HCV genotype 1 is the most prevalent. In a nationwide multicenter study spanning six years from 2016, genotype 1b emerged as the most prevalent genotype at 67%. Additionally, untypeable genotype 1 (7.7%), genotype 4 (7.3%), and genotype 3 (6.7%) were identified as the most frequently observed genotypes. Studies conducted in the Kayseri region have similarly indicated that genotype 1 is the most prevalent. However, unexpectedly, genotype 4 ranks second with an approximate rate of 30%[11-13].

Similarly, in our study, HCV genotype 1b was the most prevalent, and genotype 4 was the second most common, accounting for 19%. The prevalence of genotype 4 in our region is higher than the national HCV genotype distribution. In a study examining the global epidemiology of HCV infection, genotype 4 was identified as the dominant genotype in the Middle East[9]. This outcome may be attributed to the significant immigration influx into the Kayseri region, which is a province in Central Anatolia.

Chronic HCV infection is associated with various extrahepatic diseases, including Sjögren's syndrome, lichen planus, type 2 diabetes, and non-Hodgkin's lymphoma. Eradication of HCV has been shown to reduce liver-related and nonliver-related mortality in patients with chronic HCV[14].

With the discovery of DAA treatment after 30 years of clinical research since its identification, HCV has now become a curable disease. Clinical cure of HCV, including acute (duration of infection <6 months) and recent (duration of infection <12 months) infection, has been achieved with the revolutionary DAA therapy. Various DAA regimens are safe and effective, including modern pan-genotypic combinations, such as sofosbuvir-velpatasvir and glecaprevir-pibrentasvir[15].

In the REACT (Recently Acquired HCV Infection Trial) study, an international, multicenter, open-label, phase 3, noninferiority study, adult patients with recent HCV infection were randomly assigned to receive sofosbuvir-velpatasvir for the standard 12 weeks or a shortened six weeks. Sustainable virological response was found to be 89.4% in those receiving six weeks of treatment and 97.7% in those receiving 12 weeks. The shortened 6-week treatment was less effective than the standard 12-week treatment[16]. In a phase 3b study investigating the efficacy and safety of sofosbuvir-velpatasvir and sofosbuvir-velpatasvir-voxilaprevir, both combinations were shown to be safe and have high SVR12 rates[17]. In our study, 15 patients received sofosbuvir-velpatasvir-voxilaprevir treatment for a standard 12 weeks, and the SVR12 rate was determined to be 100%.

In contrast to the standard eight-week period for chronic HCV infection, studies have evaluated the efficacy of glecaprevir-pibrentasvir treatment over four and six weeks in patients with recent HCV infection. Treatment with glecaprevir-pibrentasvir for six weeks has proven to be effective, safe, and well-tolerated, whereas the four-week treatment regimen demonstrates less effectiveness[18,19]. In our study, 162 patients received standard glecaprevir-pibrentasvir treatment; the SVR12 rate in these patients was 100%.

Study Limitations

Our study has some limitations. Since our study was retrospective and conducted at a single center, the patients' modes of transmission and risk groups could not be evaluated.

Conclusion

In our study, the distribution of HCV genotypes aligned with national data, consisting of genotypes 1, 4, and 3, respectively. The currently employed treatment regimens for HCV infection, including sofosbuvir-velpatasvir-voxilaprevir and glecaprevir-pibrentasvir, demonstrated high effectiveness.

Ethics

Ethics Committee Approval: The study was approved by the Kayseri City Hospital of Clinical Research Ethics Committee (decision no: 870, date: 11.07.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.K.T., İ.Ç., Design: A.K.T., A.T.Ö., E.E.E., Data Collection or Processing: A.T.Ö., D.K.G., T.T., Z.B.D., M.G., Analysis or Interpretation: A.K.T., İ.Ç., Literature Search: A.K.T., D.Ç.Ö., Writing: A.K.T., İ.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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

References

1. Akar M, Solakoğlu T. Kronik hepatit C tedavisinde ikinci kuşak direk etkili oral antivirallerin gerçek yaşam verileri: Tek merkez ve heterojen hasta grubu. Akademik Gastroenteroloji Dergisi. 2020;19:123-8.
2. World Health Organization. Hepatitis C [Internet]. Hepat. C. 2022. Last accessed date: 2023 Jul 10. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c
3. Borgia SM, Hedskog C, Parhy B, Hyland RH, Stamm LM, Brainard DM, Subramanian MG, McHutchison JG, Mo H, Svarovskaia E, Shafran SD. Identification of a Novel Hepatitis C Virus Genotype From Punjab, India: Expanding Classification of Hepatitis C Virus Into 8 Genotypes. J Infect Dis. 2018;218:1722-9.
4. Çetin Duran A, Kaya Çetinkaya Ö, Sayıner AA, Şeydaoğlu G, Özkarataş E, Abacıoğlu H. Changes on Hepatitis C virus genotype distribution in Western Turkey: Evaluation of twelve-year data. Turk J Gastroenterol. 2020;31:128-35.
5. Alacam S, Bakir A, Karatas A. Hepatitis C virus genotypes and viremia in a tertiary hospital in Istanbul, Turkey. J Infect Dev Ctries. 2022;16:668-74.
6. Persico M, Aglitti A, Milella M, Coppola C, Messina V, Claar E, Gentile I, Sogari F, Pierri P, Surace LA, Morisco F, Tundo P, Brancaccio G, Serviddio G, Gatti P, Termite AP, Di Costanzo GG, Caroleo B, Cozzolongo R, Coppola N, Longo A, Fontanella L, Federico A, Rosato V, Terrenato I, Masarone M. Real-life glecaprevir/pibrentasvir in a large cohort of patients with hepatitis C virus infection: The MISTRAL study. Liver Int. 2019;39:1852-9.
7. Kaneko R, Nakazaki N, Omori R, Yano Y, Ogawa M, Sato Y. Efficacy of direct-acting antiviral treatment for chronic hepatitis C: A single hospital experience. World J Hepatol. 2018;10:88-94.
8. Ağca H, Ener B, Sağlık İ, Yılmaz E, Kazak E. Retrospective Evaluation of Hepatitis C Virus Genotypes. Türk Mikrobiyoloji Cemiy Derg. 2021;51:303-8.
9. Petruzziello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016;22:7824-40.
10. Zein NN. Clinical Significance of Hepatitis C Virus Genotypes. Clin Microbiol Rev. 2000;13:223-35.
11. Kayman T, Karakükçü Ç, Karaman A, Gözütok F. Kayseri Bölgesinde Hepatit C Virüs Enfeksiyonunun Genotip Dağılımı. Türk Mikrobiyol Cem Derg. 2012;42:21-6.
12. Altındiş M, Dal T, Akyar I, Karatuna O, Gökahmetoğlu S, Tezcan Ulger S, Kulah C, Uzun B, Sener AG, Özdemir M, Aydoğan S, Kuskucu MA, Midilli K, Otlu B, Celen MK, Buruk K, Güdücüoğlu H. Six-year distribution pattern of hepatitis C virus in Turkey: A multicentre study. Biotechnol Biotechnol Equip. 2015.
13. Sariguzel FM, Kayman T, Karaman H, Karaman A, Karakukcu C. Distribution of hepatitis C virus genotypes in Kayseri region, in Turkey: unexpected rate of genotype 4. Clin Lab. 2013;59:1403-8.
14. Tada T, Kumada T, Toyoda H, Kiriyama S, Tanikawa M, Hisanaga Y, Kanamori A, Kitabatake S, Yama T, Tanaka J. Viral eradication reduces all-cause mortality in patients with chronic hepatitis C virus infection: a propensity score analysis. Liver Int. 2016;36:817-26.
15. Martinello M, Naggie S, Rockstroh JK, Matthews GV. Direct-Acting Antiviral Therapy for Treatment of Acute and Recent Hepatitis C Virus Infection: A Narrative Review. Clin Infect Dis. 2023;77(Suppl 3):238-44.
16. Matthews GV, Bhagani S, Van der Valk M, Rockstroh J, Feld JJ, Rauch A, Thurnheer C, Bruneau J, Kim A, Hellard M, Shaw D, Gane E, Nelson M, Ingiliz P, Applegate TL, Grebely J, Marks P, Martinello M, Petoumenos K, Dore GJ; REACT study group; Protocol Steering Committee; Coordinating Centre; Site Principal Investigators. Sofosbuvir/velpatasvir for 12 vs. 6 weeks for the treatment of recently acquired hepatitis C infection. J Hepatol. 2021;75:829-39.
17. Heo J, Kim YJ, Lee SW, Lee YJ, Yoon KT, Byun KS, Jung YJ, Tak WY, Jeong SH, Kwon KM, Suri V, Wu P, Jang BK, Lee BS, Cho JY, Jang JW, Yang SH, Paik SW, Kim HJ, Kwon JH, Park NH, Kim JH, Kim IH, Ahn SH, Lim YS. Efficacy and safety of sofosbuvir-velpatasvir and sofosbuvir-velpatasvir-voxilaprevir for hepatitis C in Korea: a Phase 3b study. Korean J Intern Med. 2023;38:504-13.
18. Madsen LW, Christensen PB, Hansen JF, Røge BT, Holm DK, Dröse S, Øvrehus A. Four Weeks Treatment with Glecaprevir/Pibrentasvir + Ribavirin-A Randomized Controlled Clinical Trial. Viruses. 2022;14:614.
19. Martinello M, Orkin C, Cooke G, Bhagani S, Gane E, Kulasegaram R, Shaw D, Tu E, Petoumenos K, Marks P, Grebely J, Dore GJ, Nelson M, Matthews GV. Short-Duration Pan-Genotypic Therapy With Glecaprevir/Pibrentasvir for 6 Weeks Among People With Recent Hepatitis C Viral Infection. Hepatology. 2020;72:7-18.