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Research Article

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Viral Hepatitis Journal 2024;30(2):26-29

Are Preoperatively Requested HBsAg Results Followed?

Preoperatif İstenen HBsAg Sonuçları İzleniyor mu?

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ABSTRACT

Objectives: Hepatitis B virus (HBV), hepatitis C virus, and human immunodeficiency virus are the leading blood-borne infections. In our country, these 3 viral serologies are screened in patients scheduled for surgery. Preoperative hepatitis B surface antigen (HBsAg) screening is performed for HBV infection. In this way, patients with this virus can be detected early and receive early treatment. In this study, we aimed to investigate the rate of diagnosis and follow-up of HBV infection in patients with HBsAg positivity during preoperative serologic screening.

Materials and Methods: The HBsAg test results of patients directed to the anesthesia policlinic for preoperative preparation by surgical departments within 3 years were screened. Further examinations for HBV infection and the diagnostic status of patients found to be HBsAg-positive for the first time were analyzed.

Results: Of the 679 patients with HBsAg positivity during the 3 year study period, 412 (60.7%) had at least one previous HBsAg test in the hospital automation system. HBsAg positivity was detected for the first time in 267 (39.3%) patients. When the status of further examination was analyzed, 220 (82.4%) of 267 patients were classified as no further examination, 14 (5.2%) as incomplete further examination, and 33 (12.4%) as complete further examination.

Conclusion: The electronic patient files should be reviewed before HBsAg testing for preoperative serologic screening. HBsAg-positive patients should be directed to relevant specialty physicians for the diagnosis and treatment of HBV infection, and surgical medical science physicians should be made aware of this issue through training. In addition, it is anticipated that the "Electronic Screen Alert" application, which will guide physicians, will be useful.

Keywords: HBsAg, HBV, healthcare workers, hepatitis B virus, preoperative serologic screening, virus

ÖZ

Amaç: Hepatit B virüsü (HBV), hepatit C virüsü ve insan immün yetmezlik virüsü kan yoluyla bulaşan enfeksiyonların başında gelmektedir. Ülkemizde cerrahi planlanan hastalarda bu 3 viral seroloji taranmaktadır. HBV enfeksiyonu için ameliyat öncesi hepatit B yüzey antijeni (HBsAg) taraması yapılmaktadır. Bu sayede bu virüsü taşıyan hastalar erken tespit edilebilmekte ve erken tedavi alabilmektedir. Bu çalışmada, preoperatif serolojik tarama sırasında HBsAg pozitifliği saptanan hastalarda HBV enfeksiyonu tanı ve takip oranını araştırmayı amaçladık.

Gereç ve Yöntemler: Anestezi polikliniğine 3 yıl içinde cerrahi bölümler tarafından preoperatif hazırlık için yönlendirilen hastaların HBsAg test sonuçları tarandı. HBV enfeksiyonu için yapılan ileri tetkikler ve ilk kez HBsAg pozitif bulunan hastaların tanı durumları analiz edildi.

Bulgular: Üç yıllık çalışma döneminde HBsAg pozitifliği saptanan 679 hastanın 412'sinde (%60,7) daha önce hastane otomasyon sisteminde en az bir HBsAg testi yapılmıştı. HBsAg pozitifliği 267 (%39,3) hastada ilk kez tespit edilmiştir. İleri tetkik durumu incelendiğinde, 267 hastanın 220'si (%82,4) ileri tetkik yok, 14'ü (%5,2) eksik ileri tetkik ve 33'ü (%12,4) tam ileri tetkik olarak sınıflandırıldı.

Sonuç: Ameliyat öncesi serolojik tarama için HBsAg testi yapılmadan önce elektronik hasta dosyaları gözden geçirilmelidir. HBsAg pozitif hastalar HBV enfeksiyonu tanı ve tedavisi için ilgili uzman hekimlere yönlendirilmeli ve cerrahi tıp bilimi hekimleri eğitimlerle bu konuda bilinçlendirilmelidir. Ayrıca hekimlere yol gösterecek olan "Elektronik Ekran Uyarısı" uygulamasının faydalı olacağı öngörülmektedir.

Anahtar Kelimeler: HBsAg, HBV, sağlık çalışanları, hepatit B virüsü, ameliyat öncesi serolojik tarama, virüs

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Introduction

Hepatitis B virus (HBV) infection is the most common cause of chronic hepatitis and cirrhosis in our country. Healthcare workers are at risk of HBV infection due to occupational exposure (1). It is believed that approximately 66,000 healthcare workers develop HBV infection each year (2). Infection by healthcare workers occurs as a result of contact with blood, blood products, and body fluids infected with damaged skin and mucosa. It is also observed due to percutaneous injuries. The risk of occupational accidents leading to HBV infection transmission during surgical procedures is high. In our country, serologic screening for these three bloodborne viral infections in patients scheduled for surgical operations is performed to prevent HBV transmission to surgical personnel and detect asymptomatic HBV infection. However, there are no data on the benefits of this approach in patients with positive screening results.

In this study, we aimed to investigate the rate of diagnosis and follow-up of HBV infection in patients who were found to be hepatitis B surface antigen (HBsAg)-positive for the first time by examining patients in whom HBsAg was requested for preoperative serologic screening.

Materials and Methods

Patients who were directed to the anesthesia policlinic for preoperative preparation by surgical departments between August 2020 and August 2023 were retrospectively screened. The HBsAg test results of these patients were analyzed using the hospital automation system of the Fırat University Central Microbiology Laboratory. Further examinations for HBV infection and the diagnostic status of patients who were found to be HBsAg-positive for the first time were conducted. Further examination status was referenced by detailed HBV serology [immunoglobulin G antibody to core antigen (anti-HBc IgG), antibody to hepatitis B e antigen (anti-HBe), hepatitis B e antigen (HBeAg)] and HBV-DNA testing, and entering "B18: Chronic viral hepatitis" and other relevant diagnosis codes into the Hospital Information System according to the International Classification of Diseases (ICD)-10 criteria. After HBsAg positivity was detected for the first time, those for whom no test was ordered and no diagnosis code was entered were classified as "No further examination", those for whom some tests were ordered but no diagnosis code was entered were classified as "Incomplete further examination", and those for whom all tests were ordered and diagnosis code was entered were classified as "Complete further examination".

Enzyme-Linked ImmunoSorbent Assay method and the Architect i2000 SR (Abbott, USA) device were used to evaluate the serologic markers of the patients. Data were analyzed using SPSS package program (version 22.0, SPSS Inc., Chicago, IL). Ethics committee approval was obtained from the Fırat University Faculty of Medicine, Non-interventional Clinical Research Ethics Committee (decision number: 2023/14-19) on 14.12.2023.

Results

In the 3 year study period, 859 (2.8%) of 31,799 HBsAg test results requested before surgery were positive. Excluding repeated requests from the same patient, 679 (2.6%) of 25,978 were HBsAg-positive. The mean age of HBsAg-positive patients was 51.49±14.62 years (minimum–maximum: 1-89) and 309 (45.5%) were female. Of the 679 patients with HBsAg positivity, 412 (60.7%) had at least one previous HBsAg positivity in the hospital automation system, whereas HBsAg positivity was detected for the first time in the remaining 267 (39.3%) patients. Of the 267 patients with HBsAg positivity for the first time, 220 (82.4%) were excluded from further examination because no other tests were ordered and no diagnosis code was entered in the hospital automation system. Thirty-three (12.4%) patients who underwent further examination were classified as having complete further examination. It was determined that 28 (84.9%) of these patients were diagnosed with HBV infection, and a diagnostic code was entered. Five (15.1%) of the cases were false positives. Fourteen (5.2%) patients in whom some tests were ordered but the diagnosis code was not entered were classified as having incomplete further examination (Figure 1).

In the group of patients with incomplete further examination, only HBsAg was requested in eight (57.1%), HBV-DNA was requested in four (12.1%), and HBsAg and HBV-DNA were requested in two (16.6%) patients. Table 1 shows the status of further examination for HBV infection in patients who were found to be HBsAg-positive for the first time according to the surgical department where the operation was to be performed.

Discussion

These three viruses, which are also transmitted through the blood, pose a threat to human life and represent a public health problem. It is estimated that approximately three million exposures

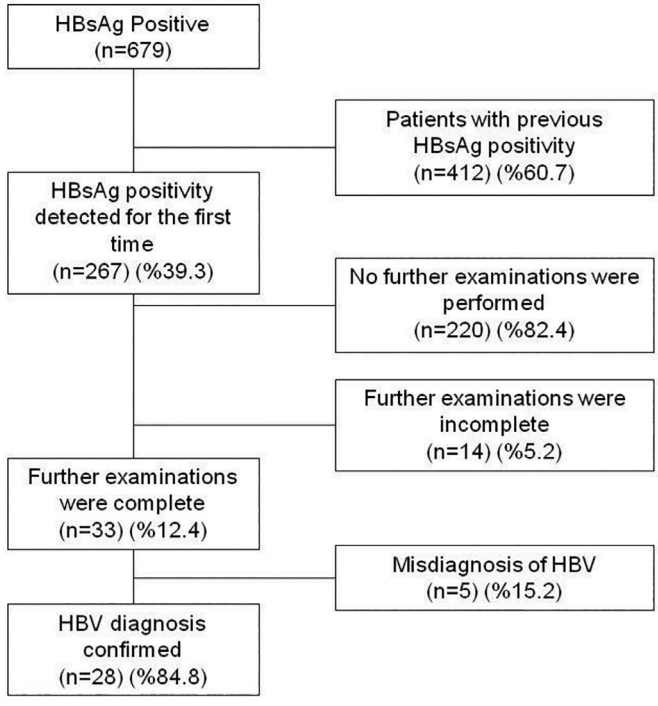

Figure 1. HBsAg-positive patients in the three-year period and further investigation status of patients with HBsAg positivity for the first time
HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen

Table 1. Status of further examination for HBV infection in patients found to be HBsAg-positive for the first time according to the surgical department where the operation was to be performed

The surgical department	No further examination n (%)	Incomplete further examination n (%)	Complete examination n (%)	Total n (%)
General Surgery	50 (80.7)	3 (4.8)	9 (14.5)	62
Urology	42 (76.4)	8 (14.5)	5 (9.1)	55
Orthopedics and Traumatology	35 (94.6)	-	2 (5.4)	37
Otolaryngology	28 (80.7)	2 (4.8)	3 (14.5)	33
Obstetrics and Gynecology	26 (78.8)	-	7 (21.2)	33
Neurosurgery	16 (89)	1 (5.5)	1 (5.5)	18
Plastic Surgery	13 (76.5)	-	4 (23.5)	17
Ophthalmology	9 (100)	-	-	9
Thoracic Surgery	1 (33.3)	-	2 (66.7)	3
Total	220 (82.4)	14 (5.2)	33 (12.4)	267

HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen

occur annually. During surgical operations, many precautions are taken to prevent the transmission of these infections to healthcare workers from the patient, as well as to healthcare workers from the patient. These measures include not using blunt suture needles, the use of reinforced gloves, changes in surgical technique, the application of less invasive alternative procedures, disinfection of the operating field after each patient, and healthcare worker training (3,4,5).

It is expected that 17 million deaths due to chronic HBV worldwide by 2030 (6). Immunization of healthcare workers and the community with an HBV vaccine is the most reliable, easy, and inexpensive method.

Learning that the patient has HBV infection before surgery will benefit both the healthcare worker and patient. From the perspective of healthcare workers, transmission from patients with high viral loads to healthcare workers will increase. If the viral load of the patient is reduced to a level that cannot be detected in the blood within the indication for treatment, the risk of transmission to healthcare workers will be significantly reduced.

From the point of view of the patient with HBV infection, the patient for whom treatment is indicated will have a chance to be treated before further liver damage develops.

It has been shown that HBV-DNA is elevated, especially in patients with HBV infection who undergo major surgical procedures, such as obesity surgery. As a result, there is a risk of severe liver damage (7,8). Again, liver function should be closely monitored in patients with HBV infection who undergo bone marrow, liver, kidney, or heart transplantation, especially during the first 6 months after surgery. In patients with elevated liver transaminases, HBV-DNA levels, liver cirrhosis characteristics, and hepatocellular carcinoma markers should be monitored (9,10,11).

The immune system is severely suppressed at various levels with intensive chemotherapy or the use of BAs, and previously silent HBV infection may lead to active hepatitis and fulminant hepatitis (12,13). In a center that implemented a warning system when an immunosuppressive agent was to be used, >90% of patients prescribed a BA underwent serologic screening to detect HBV infection. The use of the alert system increased the screening rate for HBsAg from 50% to 94% and anti-HBc from 30% to 85% in patients prescribed BAs. Six patients received prophylactic antiviral therapy, and none experienced HBV reactivation was observed in any patient (13).

In a study including data from 19,623 people aged 18-101 years in İzmir, the western city of our country, HBsAg positivity was found in 409 (2.6%) of 15,512 people, while anti-HBs positivity was found in 988 (45.65%) of 2,165 people. HBV-DNA positivity was found in 18 (4.4%) of 409 HBsAg-positive patients (14). Our study was conducted in Elazığ, an eastern province of Turkey. HBsAg positivity was detected in 679 (2.6%) of 25,978 patients aged 1-89 years who were requested preoperatively over a 3 year period. Of the 267 patients with HBsAg positivity for the first time, 220 (82.4%) were excluded from further testing because no other tests were ordered and no diagnosis code was entered in the hospital automation system. It was determined that only HBsAg was ordered in eight (57.1%), only HBV-DNA was ordered in four (12.1%), and only HBsAg and HBV-DNA were ordered in two (16.6%) patients. When these results are compared, it is observed that HBsAg positivity is 2.6% in our country. In addition, although the HBsAg test for HBV is requested preoperatively, a small benefit is obtained, and most benefits are missed because follow-up and further tests are not performed. In the literature review, no similar study was found, except for our country.

A study conducted in our country showed that the computer alert program was significantly effective in improving HBV screening rates before starting cytotoxic immunosuppressive therapies, and it was reported that the consultation rates of patients with positive HBV serology increased from 52% to 75% after the introduction of the alert system in general (15).

Another study demonstrated an improvement after the introduction of an electronic warning system called HBVision2. The HBVision2 alert system identifies patients at risk of HBV reactivation when a predetermined ICD-10 code is entered into the hospital database or when immunosuppressive treatment is prescribed. The system evaluates HBsAg and ant-HBc IgG results

and sends a warning code to the clinician for screening if serology is not fully available or indicates that a specialist should be consulted in case of positive serology (15). After the implementation of this electronic alert system, both the HBsAg (from 55.1% to 93.1%) and anti-HBc IgG screening rates increased significantly (from 4.3% to 79.4%) ($p<0.001$ for both). It was also noted that HBV reactivation developed in 2 patients (2.6%) who were not screened and/or consulted after the warning system (16).

Of the HBsAg-positive individuals (n=679), 60.7% (n=412) had previous HBsAg positivity registered in the hospital system. In order to prevent recurrent and unnecessary HBsAg test requests in hospitals, the implementation of an "Electronic Screen Warning" by information technology when requesting the HBsAg test will provide significant financial and labor gains.

In our study, only 12.4% of the patients who were found to be HBsAg-positive for the first time during preoperative screening underwent complete further examination. In 82.4% of the patients, no further tests were performed and no diagnosis was made; in 5.2%, further tests were incomplete and no diagnosis was made. The awareness of all surgical medical science physicians in our hospital regarding HBV infection and directing patients to relevant departments is quite low. Due to the constant change in research assistants, the trainings provided thus far are not sufficient. "Nosocomial infections" and "blood-borne infections" should be included in the training of research assistants in all departments.

Study Limitations

A limitation of our study is that only our hospital data were used for data analysis. Therefore, advanced tests and the diagnosis of HBV infection in foreign centers could not be performed. Another limitation was that we could not provide information about the prognosis of HBsAg-positive patients because the death/survival status of patients who did not undergo further examination was not analyzed.

Conclusion

In conclusion, healthcare professionals should approach all patients as if they have bloodborne infections by taking appropriate precautions during contact. If preoperative serologic screening is to be performed, the electronic patient file should be examined to prevent unnecessary testing, and HBV infection and immune status should be assessed. Ideally, an electronic alert system should be established, and HBsAg-positive patients should be referred to the relevant specialty physicians for the necessary diagnosis and treatment.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Fırat University Faculty of Medicine, Non-interventional Clinical Research Ethics Committee (decision number: 2023/14-19) on 14.12.2023.

Informed Consent: Patients who were directed to the anesthesia policlinic for preoperative preparation by surgical departments between August 2020 and August 2023 were retrospectively screened.

Authorship Contributions

Surgical and Medical Practices: S.K., H.H.A., Concept: N.A., A.A., Design: S.K., A.A., H.H.A., Data Collection or Processing: S.K., N.A., Analysis or Interpretation: S.K., N.A., H.H.A., Literature Search: S.K., A.A., H.H.A., Writing: S.K., N.A., A.A.

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

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Research Article

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Investigation of Hepatitis E Virus Seroprevalence and Chronic Hepatitis E Infection in HIV-Positive Patients

HIV Pozitif Hastalarda Hepatit E Virüs Seroprevelansı ve Kronik Hepatit E Enfeksiyonunun Araştırılması

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ABSTRACT

Objectives: This study aimed to investigate the seroprevalence of hepatitis E virus (HEV) and chronic HEV infection in patients with confirmed human immunodeficiency virus (HIV)-1 infection.

Materials and Methods: This prospective single-center study included a sample of 101 patients aged 18-84 years who were admitted to Hatay Mustafa Kemal University Hospital between May 2022 and December 2022 with a confirmed diagnosis of HIV-1 infection. From the blood samples collected for the study, anti-HEV immunoglobulin M (IgM) [HEV IgM enzyme-linked immunosorbent assay (ELISA), DiaPro, Italy] and anti-HEV immunoglobulin G (IgG) (HEV IgG ELISA, DiaPro, Italy) were evaluated using the microplate ELISA method. Ribonucleic acid (RNA) was extracted from plasma samples using a Qiagen virus kit (Qiagen EZ1 automated system, Germany). HEV-RNA was tested using an in-house reverse transcription polymerase chain reaction for all samples included in the study. In addition, HIV-RNA, CD4+T cell count, hepatitis B surface antigen (HbsAg), anti-hepatitis C virus (HCV), anti-hepatitis A virus (HAV) IgG, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (TBIL), and venereal disease research laboratory (VDRL) parameters were obtained from the hospital automation system.

Results: Anti-HEV IgG seropositivity was 3.96% (n=4). HEV-RNA was analyzed from all samples, but no HEV-RNA positivity was detected. There was no significant difference between the anti-HEV IgG (+) and anti-HEV IgG (-) group in terms of HIV-RNA level, CD4+T cell count, ALT, AST, alkaline phosphatase, gamma-glutamyl

ÖZ

Amaç: Bu çalışmada, insan immün yetmezlik virüsü (HIV)-1 enfeksiyonu doğrulanmış hastalarda hepatit E virüsü (HEV) ve kronik HEV enfeksiyonunun seroprevalansının araştırılması amaçlandı.

Gereç ve Yöntemler: Bu prospektif ve tek merkezli çalışma, Mayıs 2022 ile Aralık 2022 tarihleri arasında Hatay Mustafa Kemal Üniversite Hastanesi'ne HIV-1 enfeksiyonu tanısı doğrulanmış olarak başvuran 18-84 yaş arası 101 hastadan oluşan bir örneklemi içermektedir. Çalışma için alınan kan örneklerinden, mikroplaka kullanılarak anti-HEV immünoglobulin M (IgM) [HEV IgM enzim bağlantılı immünosorbent tahlili (ELISA), DiaPro, İtalya] ve anti-HEV IgG (HEV IgG ELISA, DiaPro, İtalya) ELISA yöntemi çalışıldı. Plazma örneklerinden ribonükleik asit (RNA) ekstraksiyonu, bir Qiagen virüs kiti (Qiagen EZ1 otomatik sistemi, Almanya) kullanılarak gerçekleştirildi. HEV-RNA, çalışmaya dahil edilen tüm numunelerde kurum içi ters transkripsiyon polimeraz zincir reaksiyonu testi kullanılarak test edildi. Ayrıca HIV-RNA, CD4+T hücre sayısı, hepatit B yüzey antijeni (HbsAg), anti-hepatit C virüsü (HCV), anti-hepatit A virüsü (HAV) IgG, aspartat transaminaz (AST), alanin transaminaz (ALT), total bilirubin (TBİL) ve zührevi hastalıklar araştırma laboratuvarı (VDRL) parametreleri hastane otomasyon sisteminden elde edildi.

Bulgular: Anti-HEV IgG seropozitifliği %3,96 (n=4) olarak belirlendi. Tüm örneklerde HEV-RNA analizi yapıldı ancak HEV-RNA pozitifliği saptanmadı. Anti HEV IgG (+) grupla, anti HEV IgG (-) grup arasında HIV-RNA düzeyi, CD4+T hücre sayısı, ALT, AST, alkaline

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transpeptidase, and TBIL levels. Anti-HAV IgG seropositivity was observed in 89.1% (n=90) of the patients included in our study, HbsAg seropositivity was observed in 1.0% (n=1), and HCV seropositivity was not observed. VDRL seropositivity was observed in 11.9% (n=12) of the patients.

Conclusion: Although our findings showed that HEV seroprevalence was not high in HIV-positive patients and did not develop into chronic infection, we believe that multicenter studies with a larger number of patients are needed to investigate the relationship between HIV and HEV in our country.

Keywords: HIV, hepatitis E virus seroprevalence, chronic hepatitis E infection

phosphatase, gama-glutamil transferaz ve TBİL düzeyleri açısından anlamlı fark yoktu. Çalışmamıza dahil edilen hastalarda anti-HAV IgG seropozitifliği %89,1 (n=90), HBsAg seropozitifliği pozitifliği %1,0 (n=1) seropozitifliği gözlendi ancak HCV seropozitifliği görülmedi. VDRL seropozitifliği %11,9 (n=12) görüldü.

Sonuç: Bulgularımız HIV pozitif hastalarda HEV seroprevalansının yüksek olmadığını ve kronik enfeksiyona dönüşmediğini gösterse de ülkemizde HIV ile HEV arasındaki ilişkinin araştırılması için daha fazla sayıda hasta ile çok merkezli çalışmalara ihtiyaç olduğu kanaatindeyiz.

Anahtar Kelimeler: HIV, hepatit E virüs seroprevelans, kronik hepatit E enfeksiyonu

Introduction

Although hepatitis E virus (HEV) infection is a disease that occurs worldwide, its prevalence is higher in the least developedand developing countries (1,2). Although HEV infection usually results in an acute and self-limiting clinical course, pregnancy, young age, chronic liver disease, solid organ transplantation, and human immunodeficiency virus (HIV) infection, and so forth. It can be severe in the high-risk groups. In addition, HEV infection can become chronic in immunocompromised patients (solid organ transplantation, HIV-positive patients with a CD4+T cell count <200 cells/mm^3), and this situation is more common in developed countries (3). Many studies have shown that HEV seroprevalence in HIV-positive patients is different (high, same, and low) compared with the healthy population (4,5,6,7). Many studies on HEV seroprevalence (covering the non-HIV population) have been conducted in Turkey. In a comprehensive meta-analysis of these studies, HEV seroprevalence was reported to be 0-12.4% on average (8). In our literature review, we found that very few studies have investigated the relationship between HEV and HIV in our country. In addition, chronic HEV infection and genotype analysis were not performed in HIV-positive patients. Therefore, large-scale studies are needed. For these reasons, we investigated the seroprevalence of HEV in HIV-positive patients to determine the presence of chronicity and performed HEV genotype analysis.

Materials and Methods

This prospective single-center study included a sample of 101 patients aged 18-84 years who were admitted to Hatay Mustafa Kemal University Hospital between May 2022 and December 2022 with confirmed diagnoses of HIV-1 infection. We included 50 patients whose HIV-1 infection diagnosis was confirmed and who had not yet started treatment and 51 patients whose HIV-1 infection diagnosis was confirmed at least 6 months previously and who were receiving treatment. After obtaining written consent from the patients selected on a voluntary basis, we recorded their demographic and clinical characteristics and laboratory findings.

The inclusion criteria were patients followed up with a diagnosis of HIV-1 and those who provided written consent. Patients younger than 18 years were not included in the study.

We obtained blood samples from the patients; 5 mL was placed in a yellow-capped gel biochemistry tube, and 4 mL was placed in a purple EDTA hemogram tube. The samples were centrifuged within 30 minutes at 4,000 rpm for 10 minute. Serum and plasma samples were separated into Eppendorf tubes and stored at -80 °C until the day of study. All samples were sent to the Ankara General Directorate of Public Health, National HIV/AIDS and Viral Hepatitis Microbiology Reference Laboratory. In this study, anti-HEV immunoglobulin M (IgM) [HEV IgM enzyme-linked immunsorbent assay (ELISA), DiaPro, Italy] and anti-HEV immunoglobulin G (IgG) (HEV IgG ELISA, DiaPro, Italy) were evaluated using the microplate ELISA method. We extracted ribonucleic acid (RNA) from plasma samples using a Qiagen virus kit (Qiagen EZ1 automated system, Germany). HEV-RNA was tested using an in-house reverse transcription polymerase chain reaction test for all samples included in the study. In addition, HIV-RNA, CD4+T cell count, hepatitis B surface antigen (HbsAg), anti-hepatitis C virus (HCV), anti-hepatitis A virus (HAV) IgG, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (TBIL), and venereal disease research laboratory (VDRL) parameters were obtained from the hospital automation system.

Statistical Analysis

We used IBM SPSS Statistics version 22.0 package for thethe statistical analysis of the data. We evaluated the compliance of continuous data with the assumption of normality according to the Kolmogorov-Smirnov test and coefficient of variation. Categorical measurements were given as numbers and percentages, continuous measurements with non-normal distribution were given as median (minimum-maximum) or median (interquartile range: 25th-75th percentiles), and continuous measurements with normal distribution were given as mean and standard deviation. We used Pearson's chi-square test or Fisher's exact test statistics to compare categorical measurements between groups. For the pairwise comparisons of groups, we used the Mann-Whitney U test if the assumptions were not met and the independent-sample (Student) t-test if the assumptions were met. In all the tests, the statistical significance level was set at 0.05.

We conducted this study to investigate HEV seroprevalence and chronic HEV infection in HIV-positive patients. This study was conducted with the permission of the Mustafa Kemal University Faculty of Medicine Clinical Research Ethics Committee (approval number: 2022/52, date: 09.05.2022) and funding provided by Scientific Research Projects (project number: 22.TU.010).

Results

Of the 101 patients diagnosed with HIV-1 included in our study, 78 (77.2%) were male and 23 (22.8%) were female, and the median age was 32 years. We found no significant difference in gender or age between the new diagnosis group and the old diagnosis group (p=0.582 and p=0.257, respectively) (Table 1).

Although anti-HEV IgM positivity was not detected in any of the blood samples and anti-HEV IgG seropositivity was low (3.96%), we analyzed HEV-RNA from all samples. However, HEV-RNA positivity was not detected in any of the samples. Because HEV-RNA positivity was not detected in our study, we could not perform HEV genotype analysis. The reason for testing HEV-RNA in all patients who are anti-HEV IgM and IgG negative, as well as in patients who are anti-HEV IgG-positive, is that these patients are also HIV positive. As is well known, antibodies such as IgM and/or IgG might not be detected in immunosuppressed patients. We applied polymerase chain reaction to all of our patients with the idea that we could detect HEV-RNA in our patients with negative antibodies. Although thethe anti-HEV IgG (+) rate was 13.0% in women, it was 1.3% in men. Of the 50 patients in the new diagnosis group, anti-HEV IgG positivity was detected in two patients (4.0%); among the 51 patients in the old diagnosis group, anti-HEV IgG positivity was detected in 2 (3.9%). Because of the small number of patients, we could not perform significance testing. Table 2 presents a summary of the comparison of demographic and clinical characteristics between anti-HEV IgG-positive and anti-HIV (+) cases.

Table 3 summarizes the laboratory parameters of the anti-HEV IgG-positive and -negative HIV (+) cases. There was no significant difference between the anti-HEV IgG (+) group and the anti-HEV IgG (-) group in terms of HIV-RNA level, CD4+T cell count, ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and TBIL levels (p=0.528, p=0.573, p=0.313, p=0.432, p=0.474, p=0.243, and p=0.413, respectively).

Table 1. Comparison of the age and sex characteristics of the patients

Variables		Total (n=101)	New diagnosis (n=50)	Old diagnosis (n=51)	p-value
Age (year), (median, min.-max.)		32 (19-84)	33 (19-84)	32 (19-67)	0.582*
Gender n (%)	Male	78 (77.2)	41 (82.0)	37 (72.5)	0.257**
	Female	23 (22.8)	9 (18.0)	14 (27.5)	

*Mann-Whitney U test, **Pearson's chi-square test, n: Number, min.: Minimum, max.: Maximum

Table 2. Comparison of demographic and clinical characteristics between anti-HEV IgG-positive and anti-HIV (+) cases

Variables	Anti-HEV IgG (+) (n=4)	Anti-HEV IgG (-) (n=97)	p-value*
Age, year	56.0 (47.5-62.0)	32.0 (27.0-42.0)	0.011
Sex, n (%)			
Male Female	1 (25.0) 3 (75.0)	77 (79.3) 20 (20.7)	0.002
Newly diagnosed HIV (+) cases, n (%)	2 (50.0)	48 (49.5)	0.984
Foreign nationals, n (%)	0 (0)	7 (7.2)	0.578
MSM + bisexuality, n (%)	0 (0)	44 (45.4)	0.073
Education level (High School/University), n (%)	1 (25.0)	61 (62.9)	0.127
Additional disease, n (%)	1 (25.0)	11 (11.3)	0.408
Smoking, n (%)	1 (25.0)	40 (39.6)	0.517
Alcohol use, n (%)	0 (0)	28 (28.9)	0.206
Foreign travel history, n (%)	0 (0)	11 (11.3)	0.476
Coinfection rate, n (%)			
Anti-HAV IgG (+) HBsAg (+) VDRL (+) Anti-HCV (+)	2 (50.0) 0 (0) 0 (0) 0 (0)	88 (90.7) 1 (1.0) 14 (14.4) 0 (0)	0.010 0.838 0.413
CD4+T cell status			
<200 cells/µL 200-499 cells/µL ≥500 cells/µL	0 (0) 3 (75.0) 1 (25.0)	7 (7.2) 70 (72.2) 20 (20.6)	0.849

Continuous measurements that did not comply with normal distribution were expressed as median (interquartile range: 25th-75th percentiles).
n: Number, HIV: Human immunodeficiency virus, MSM: Man who have sex with man, anti-HAV IgG: Hepatitis A virus antibody test immunoglobulin G, HBsAg: Hepatitis B surface antigen, VDRL: Venereal disease research laboratory, anti-HCV: Hepatitis C virus antibody test, anti-HEV: Hepatitis E virus antibody test, *Pearson's chi-square test vena Fisher's exact test

One of the 101 patients included in our study (1.0%) was HbsAg-positive. This patient was in the new diagnostic group. In our study, none of the patients tested positive for anti-HCV antibodies. In our study, anti-HAV IgG was positive in 90 (89.1%) patients. Anti-HAV IgG was positive in 44 (88.0%) patients in the new diagnosis group and in 46 (90.2%) patients in the old diagnosis group. No significant difference was detected between the groups in terms of anti-HAV IgG positivity (p=0.723). In our study, 12 (11.9%) patients were VDRL-positive. VDRL positivity was detected in seven (14.0%) patients in the new diagnostic group and in five (9.8%) patients in the old diagnostic group. We found no significant difference between the groups regarding VDRL positivity (p=0.515). Table 4 presents a comparison of hepatitis co-infection and VDRL test results between the patient groups.

Discussion

In the HEV seroprevalence study conducted in our country with 114 HIV-positive volunteers at Sakarya University in 2019, seropositivity was reported to be 4%, which is similar to our study (9). In addition, although all anti-HEV IgG-positive patients in that study were male, in our study the anti-HEV IgG (+) rate was 13.0% in females and 1.3% in males. In another study conducted in Uganda, the authors found anti-HEV IgG seropositivity found to be similar between volunteers with and without HIV, and they reported that there was no difference in age gender distribution (7). In studies conducted in our country and in Uganda, the median age of anti-HEV IgG (+) cases was similar to that of the anti-HEV IgG (-) group, being significantly higher. The reason for the high age in the studies conducted in our country and Uganda might be due to the high probability of encountering HEV over time due to fecal-oral transmission.

A study conducted in HIV-negative volunteers [including HIV-negative men who have sex with men (MSM)] in Italy showed that sexual transmission of HEV was unlikely and had no impact on HEV prevalence (10). In another study conducted in the Netherlands, the authors reported that there was no significant relationship between MSM sexual habit and HEV seropositivity in HIV-positive patients (11). In our study, we did not detect HEV in individuals with MSM sexual habits, which supports the findings of studies conducted in Italy and the Netherlands.This might be because of the lack of sexual transmission of HEV.

There are also studies in the literature investigating anti-HEV IgG seropositivity in HIV-positive pregnant women (12,13). The fact that anti-HEV IgG was found to be negative in all three pregnant patients in our study can be explained by the small number of patients. To determine the level and/or relationship of HEV seropositivity, especially in HIV-positive pregnant women in Turkey, further studies are needed. We recommend that multicenter studies with a higher number of patients be conducted in Turkey to determine the relationship between HEV seropositivity levels, especially in HIV-positive pregnant women.

In addition, in our study, we investigated the seroprevalence of VDRL, HbsAg, anti-HCV, and anti-HAV IgG in HIV-positive patients, and the results we found were similar to those of another study conducted in our country (14). However, further studies with larger patient series are required to clarify this issue.

Table 3. Comparison of laboratory parameters between anti-HEV IgG-positive and anti-HIV (+) cases

Variables	Anti-HEV IgG (+) (n=4)	Anti-HEV IgG (-) (n=97)	p-value
HIV-RNA (copies/mL)	10115 (0-50119)	0 (0-346100)	0.528
CD4+T number, cells/µL	404.5 (357.5-514.5)	398.0 (300.0-452.0)	0.573
AST, U/L	17 (13.5-27.5)	24 (16-31)	0.313
ALT, U/L	20 (14.5-29.0)	25 (18-33)	0.423
ALP, U/L	100.5 (73.5-130.5)	112 (96-129)	0.474
GGT, U/L	37 (30.5-47.5)	31 (23-40)	0.243
TBIL, mg/dL	0.125 (0.115-0.165)	0.180 (0.110-0.210)	0.413

Continuous measurements that did not comply with normal distribution were expressed as median (interquartile range: 25th-75th percentiles).
Anti-HEV IgG: Hepatitis E virus antibody test immunoglobulin G, HIV-RNA: Human immunodeficiency virus-ribonucleic acid, AST: Aspartate aminotransferase, ALT: Alkaline aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, TBIL: Total bilirubin

Table 4. Comparison of hepatitis co-infection and VDRL test results between patient groups

Variables		Total (n=101)	New diagnosis (n=50)	Old diagnosis (n=51)	p-value*
HBsAg n (%)	Positive	1 (1.0)	1 (2.0)	0 (0.0)	0.495
	Negative	100 (99.0)	49 (98.0)	51 (100.0)	
Anti HCV n (%)	Positive	0 (0.0)	0 (0.0)	0 (0.0)	-
	Negative	101 (100.0)	50 (100.0)	51 (100.0)	
Anti-HAV IgG n (%)	Positive	90 (89.1)	44 (88.0)	46 (90.2)	0.723
	Negative	11 (10.9)	6 (12.0)	5 (9.8)	
VDRL n (%)	Positive	12 (11.9)	7 (14.0)	5 (9.8)	0.515
	Negative	89 (88.1)	43 (86.0)	46 (90.2)	

n: Number, *Pearson's chi-square test vena Fisher's exact test, HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virüs, HAV: Hepatitis A virüs, VDRL: Venereal disease research laboratory

In our study, the fact that anti-HEV IgG (+) was not found in any of the seven (6.9%) HIV (+) cases with a CD4+T cell count <200 cells/μL is incompatible with the literature. In contrast, studies conducted in various countries around the world have reported a correlation between HIV and HEV seroprevalence, but this correlation was independent of the CD4+T cell count. For example, a study involving 251 HIV-positive patients in Iranfoundno relationship between CD4+T cell count and HEV seropositivity (4). Similarly, in a study conducted in China with 639 HIV-positive cases, the authors found that HEV seropositivity (39.4%) was higher than that in the healthy population (15). In our study, the fact that we did not find anti-HEV IgG (+) in any of the seven cases with a CD4+T cell count <200 cells/μL is, in our opinion, due to the small number of cases.

In our study, the anti-HEV IgG (+) level was significantly higher in the anti-HEV IgG (-) group than in the anti-HEV IgG (+) group (90.7% and 50%, respectively, p=0.010), which is similar to a study conducted in our country (9). The seroprevalence of HAV and HEV is strongly associated with socioeconomic conditions and similar transmission routes (fecal-oral), especially due to war, natural disasters, and so forth, as well as migration from developing countries to developed countries. It has been suggested thatcher HAV and HEV seroprevalence is likely to increase in developed countries (16). In our study, our finding that anti-HEV IgG (+) levels were significantly higher in the anti-HEV IgG (-) group than in the anti-HEV IgG (+) group is important. This situation raises the question of whether cross-immunity against HEV infection occurs in those who have previously had an HAV infection. The second question is whether anti-HAV IgG protects against HEVs or not in cross-immunity. Considering the ages at which these two infections were acquired, it is more likely that HAV infection was acquired in childhood in both our country and other countries around the world, and anti-HAV IgG positivity is protective against HEV. However, because of the small number of individuals with positive anti-HEV IgG antibodies in our study, this argument remains weak. In other words, in this study conducted in Hatay, comprehensive studies are needed to understand whether anti-HAV IgG seropositivity is inversely proportional to anti-HEV IgG seropositivity.

We found no significant difference in HIV-RNA levels, CD4 count, ALT, AST, ALP, GGT, and TBIL levels between the anti-HEV IgG (+) group and the anti-HEV IgG (-) group, and this result is similar to that of another study conducted in our country (9).

Studies conducted in immunosuppressed patients or those receiving chemotherapy/immunotherapy due to immunosuppression (e.g., solid organ transplantation, bone marrow transplantation, lymphoma) have demonstrated the presence of chronic HEV infection. Although studies have shown that HEV infection becomes chronic in HIV-positive patients, this phenomenon remains a mystery. In these studies, chronic HEV infection was found to be predominantly associated with genotype 3, but some studies have shown that genotypes 4 and genotype 7 also cause chronic infection (17,18,19,20). Chronic HEV infection has not been investigated in HIV-positive patients in our country. Although one of the most important aims of our study was to investigate chronic HEV infection in HIV-positive patients and perform genotype analysis, chronic HEV infection was not detected, and genotype analysis could thus not be performed. Although our study has some limitations, our findings suggest that HEV does not become chronic in HIV-positive patients and does not pose a problem for these patients, and more studies are needed.

Study Limitations

The small number of patients and data obtained from a single center is among the limitations of this study.

Conclusion

We conducted this study to investigate HEV seroprevalence in HIV-positive patients, determine whether HEV develops into a chronic infection, and perform genotype analysis. We found that the HEV seropositivity (anti-HEV IgG) was low at a rate of 3.96%. Although anti-HEV IgM was negative and anti-HEV IgG was positive at a low rate in all patient samples, we studied HEV-RNA in all samples and did not detect HEV-RNA positivity in any of the samples. Therefore, we could not perform genotype analysis. Our results show that HEV seroprevalence is low in HIV-positive patients, there is no evidence of chronic infection, and this does not pose a problem for HIV-positive patients. To investigate the relationship between HIV and HEV in our country, more studies with a larger number of patients are needed. In addition, we propose that studies should be conducted to investigate the seroprevalence of VDRL, HbsAg, anti-HCV, and anti-HAV IgG in HIV-positive patients as secondary results in our study, and these patients should be treated, followed up, and vaccinated if necessary.

Ethics

Ethics Committee Approval: This study was conducted with the permission of the Hatay Mustafa Kemal University Faculty of Medicine Clinical Research Ethics Committee (approval number: 2022/52, date: 09.05.2022).

Informed Consent: Informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: H.Y., Y.Ö., M.Ç., T.D., Concept: H.Y., Y.Ö., M.Ç., T.D., Design: H.Y., Y.Ö., T.D., Data Collection or Processing: H.Y., M.Ç., Analysis or Interpretation: H.Y., M.Ç., Literature Search: H.Y., Y.Ö., M.Ç., T.D., Writing: H.Y., Y.Ö., M.Ç., T.D.

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Research Article

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Real-World Data on the Use of Glecaprevir/Pibrentasvir in the Treatment of Hepatitis C: Is Shorter Treatment Possible?

Hepatit C Tedavisinde Glekaprevir/Pibrentasvir'in Gerçek Dünya Verileri: Daha Kısa Tedavi Mümkün mü?

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ABSTRACT

Objectives: This study aimed to present real-world data on the efficacy of glecaprevir/pibrentasvir (G/P) in chronic hepatitis C (CHC) patients treated at our center.

Materials and Methods: Non-cirrhotic, treatment-naive, and treatment-experienced (TN/TE) CHC patients with CHC who started G/P treatment in 2022 were included in this retrospective, cross-sectional, single-center, national study. Sustained virological response (SVR) was defined as undetectable hepatitis C virus-ribonucleic acid (HCV-RNA) for at least 12 weeks following the discontinuation of antiviral therapy.

Results: Sixty patients with non-cirrhotic TN/TE CHC who started G/P were included in the study. All patients received G/P treatment for 8 weeks. The median age of the patients was 45 years (interquartile range 22-3) and 44 (73.3%) were males. The most frequently identified risk factor for CHC was substance use (n=7, 11.7%), whereas the most common comorbidities were cardiovascular disease, hypertension (n=8,13.3%), and diabetes mellitus (n=7, 11.7%). HCV genotype was evaluated in all patients. Genotype distribution: Genotype 1b was detected in 53 patients (88.3%) and genotype 1 was detected in 7 patients (11.7%). The median pretreatment HCV-RNA level of the patients was 137,000 IU/mL. HCV-RNA was evaluated in all patients at the 4th and 8th weeks of treatment and at the 12th week after treatment. All patients were HCV-RNA-negative in the 1st month of treatment.

ÖZ

Amaç: Bu çalışmanın amacı, merkezimizde tedavi edilen kronik hepatit C (KHC) hastalarında glekaprevir/pibrentasvir (G/P) etkinliğine ilişkin gerçek dünya verilerini sunmaktır.

Gereç ve Yöntemler: Bu retrospektif, kesitsel, tek merkezli, ulusal çalışmaya 2022 yılında G/P tedavisine başlayan sirotik olmayan, tedavi naif ve tedavi deneyimli (TN/TE) koroner kalp hastalığı (KKH) hastaları dahil edilmiştir. Kalıcı virolojik yanıt (KVY), antiviral tedavinin kesilmesini takiben en az 12 hafta boyunca tespit edilemeyen hepatit C virüsü-ribonükleik asit (HCV-RNA) olarak tanımlanmıştır.

Bulgular: Çalışmaya G/P başlanan sirotik olmayan TN/TE KHC'li 60 hasta dahil edilmiştir. Tüm hastalar 8 hafta boyunca G/P tedavisi almıştır. Hastaların ortanca yaşı 45 (çeyrekler arası aralık 22-3) ve 44'ü (%73,3) erkekti. KKH için en sık tanımlanan risk faktörü madde kullanımı (n=7, %11,7) iken, en yaygın komorbiditeler kardiyovasküler hastalık, hipertansiyon (n=8, %13,3) ve diabetes mellitus (n=7, %11,7) idi. Tüm hastalarda HCV genotipi değerlendirilmiştir. Genotip dağılımı: 53 hastada (%88,3) genotip 1b ve 7 hastada (%11,7) genotip 1 saptandı. Hastaların tedavi öncesi medyan HCV-RNA düzeyi 137.000 IU/mL idi. HCV-RNA tüm hastalarda tedavinin 4. ve 8. haftalarında ve tedaviden sonraki 12. haftada değerlendirilmiştir. Tüm hastalar tedavinin 1. ayında HCV-RNA negatifti. Ayrıca, tedavi sonunda ve 12 haftalık takipte tüm hastalarda HCV-RNA negatifliği devam etmiştir. Tedavi sırasında

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Additionally, HCV-RNA negativity continued in all patients at the end of treatment and at 12 week follow-up. No mild, moderate, or serious adverse events were observed during or after treatment. All patients were successfully treated.

Conclusion: All patients extremely well tolerated the drug. The SVR response was found to be 100%. In addition, the fact that the viral load of all patients in our study was negative in the 4th week of treatment suggested the possibility of shorter-term treatment. More studies on this subject.

Keywords: Hepatitis C, real-life data, treatment responses

veya sonrasında hafif, orta veya ciddi advers olay gözlenmemiştir. Tüm hastalar başarıyla tedavi edilmiştir.

Sonuç: Tüm hastalar ilacı son derece iyi tolere etmiştir. KVY yanıtı %100 olarak bulunmuştur. Ayrıca, çalışmamızdaki tüm hastaların viral yükünün tedavinin 4. haftasında negatif olması, daha kısa süreli tedavi olasılığını düşündürmüştür. Bu konuda daha fazla çalışma yapılmalıdır.

Anahtar Kelimeler: Hepatit C, gerçek yaşam verileri, tedavi yanıtları

Introduction

Globally, an estimated 58 million people have chronic hepatitis C virus (CHC) infections, and approximately 1.5 million new infections occur each year. The World Health Organization (WHO) estimates that approximately 290,000 people died from hepatitis C in 2019, mostly from cirrhosis and hepatocellular carcinoma (1). The elimination of viral hepatitis has been accepted as a public health goal by the World Health Assembly for 2030 (2). After the first direct-acting antivirals (DAAs) were approved by the US Food and Drug Administration in 2011, more than 10 pharmaceuticals (including those effective against all genotypes) are currently available. The WHO recommends pan-genotypic DAA agents for all adult patients infected with hepatitis C virus (HCV) (1).

Glecaprevir/pibrentasvir (G/P) is a fixed-dose combination of the HCV NS3/4A protease inhibitor G and the HCV NS5A inhibitor P. They are DAA agents with pangenotypic activity and a high resistance barrier. The recommended G/P dose is 300/120 mg (three tablets of 100 mg/40 mg) once a day with food (3). G/P has been shown to be highly effective and tolerable in various studies (4,5,6). Guidelines now recommend pan genotypic effective regimens for simplified HCV treatment in patients with cirrhosis and compensated cirrhosis (CC) (7,8). G/P was shown to have a positive safety profile in a phase 3 study conducted in treatment-experienced (TE) or treatment-naive (TN) patients with chronic HCV genotypes 1, 2, 4, 5, or 6 infection and CC (9).

Nowadays, we are talking about cure because of the new generation DAAs, which are very effective against CHC. In this study, we aimed to present our real-life data on G/P in non-cirrhotic, TE/TN CHC patients and to examine whether shorter-term treatment is possible.

Materials and Methods

This retrospective, cross-sectional, single-center, and national study included 60 patients who received G/P treatment at our hospital in 2022. Patients' data [sociodemographic characteristics (age, gender, mode of transmission), laboratory (viral load, HCV genotype-subtype, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), platelet, international normalized ratio, alpha fetoprotein (AFP), total bilirubin) and radiological findings before and during treatment, treatment-related side effects and comorbidities] were retrospectively collected.

Non-cirrhotic, TN/TE patients aged >18 years, infected with genotypes 1 and 1b of HCV for more than six months were included in the study. Considering national and international guidelines, all non-cirrhotic patients with TN/TE were treated with three tablets of G/P per day with food for 8 weeks (3,10). Patients were evaluated in terms of clinical, virological, and biochemical improvement and adverse events in the fourth, eighth, and twelfth weeks of treatment. Follow-up of patients whose treatment was completed was continued every 3 months to determine sustained virological response (SVR).

SVR was defined as undetectable HCV-ribonucleic acid (RNA) for at least 12 weeks after the end of antiviral therapy. The primary endpoint was SVR achievement. The secondary endpoints were virological responses at week four and at the end of treatment (eighth or twelfth week).

Statistical Analysis

IBM SPSS 21.0 for Windows statistical package was used for the statistical evaluation of the research data. Quantitative variables are presented as mean ± standard deviation, and categorical variables are presented as number and percentage (%). The Kolmogorov-Smirnov test was used to determine whether the data conformed to the normal distribution. Not normally distributed; Friedman test was used to compare the baseline, 4th, 8th, and 12th week data. The hypotheses were two-sided; a statistically significant result was accepted if $p \leq 0.05$.

Ethical Permission

This study was approved by the Dicle University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (approval number: 242, date: 13.09.23).

Results

This study included 60 patients with non-cirrhotic, TN/TE, CHC who were treated with G/P for 8 weeks at our hospital in 2022. The baseline characteristics and pretreatment laboratory results of all patients are presented in Table 1. The median age of the patients was 45 years (interquartile range 22-73) and 44 (73.3%) were males. The most frequently identified risk factor for CHC in the study population was substance use (n=7, 11.7%), whereas the most common comorbidities were cardiovascular disease, hypertension (n=8, 13.3%), and diabetes mellitus (n=7, 11.7%). HCV genotype was evaluated in all patients. Genotype distribution: Genotype 1b was detected in 53 patients (88.3%) and genotype 1 was detected in 7 patients (11.7%).

Laboratory data before treatment and changes in parameters during the first month of treatment and at the end of treatment

are presented in Table 2. The results of patients whose laboratory parameters were recorded during all three periods were analyzed. No statistically significant differences were found in the parameters ALT, AST, GGT, AFP, albumin, ALP, total bilirubin, and platelet and prothrombin time, which are evaluated as biomarkers for liver health at the beginning, 4th week, and end of treatment.

The median pre-treatment HCV-RNA level of all patients was 137,000 IU/mL. HCV-RNA was evaluated in all patients at the 4th and 8th weeks of treatment and at the 12th week after treatment. In the first month of treatment, all patients were HCV-RNA-negative. In addition, HCV-RNA negativity continued in all patients at the end

Table 1. Baseline characteristics of patients before treatment

	n=60
Age > year, median (IQR)	45 (22-73)
Sex, n (%)	
Male Female	44 (73.3) 16 (26.7)
Risk factors, n (%)	
Substance abuse Blood products Surgical contamination Unknown	7 (11.7) 5 (8.3) 6 (10) 41 (68.3)
Comorbidities, n (%)	
Diabetes mellitus Hypertension Heart disease Substance abuse Alcohol	7 (11.7) 8 (13.3) 8 (13.3) 3 (5) 3 (5)
Genotype, n (%)	
Gp1 Gp1b	7 (11.7) 53 (88.3)
Pretreatment laboratory data	
HCV-RNA level, IU/mL; median (IQR) Platelets, x10^3/µL Prothrombin time Creatinine, mg/dL Albumin, g/dL ALT, U/L AST, U/L GGT, U/L ALP, U/L Total bilirubin level, mg/dL AFP, IU/mL	137.000 (3780-810.900) 212.000 (110000-290000) 14.4 (11.1-16.1) 1.1 (0.5-1.6) 3.2 (2.9-4.4) 36 (25-56) 44 (21-54) 32 (25-50) 108 (72-131) 1.1 (0.7-1.6) 3.1 (1.2-3.4)
Treatment duration	
8 weeks, n (%)	60 (100)
Treatment experience n (%)	
No Yes PEG + RBV Ombitasvir/paritaprevir/ritonavir + dasabuvir Telaprevir + PEG + RBV	27 (45) 33 (55) 22 (36.7) 10 (16.7) 1 (1.7)

IQR: Interquartile range, HCV: Hepatitis C virus, RNA: Ribonucleic acid, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, AFP: Alpha-fetoprotein, PEG: Pegile interferon, RBV: Ribavirin

Table 2. Pre-treatment, 1st-2nd month of treatment, and post-treatment laboratory data

	Pretreatment values		**4 week**		**8 week**		**12 week**		
	x ± SD	**Median (IQR) (min.-max.)**	**X + SD**	**Median (IQR) (min.-max.)**	**x + SD**	**Median (IQR) (min.-max.)**	**x + SD**	**Median (IQR) (min.-max.)**	**p***
HCV-RNA	962.415±1724604	137000 (3780-8109000)	-	-	-	-	-	-	**0.000**
Platelets	204.4±42.2	212 (110-290)	202.15±52.053	189.5 (110-345)	204.38±50.817	212 (110-389)	185.92±41.885	178 (110-290)	0.456
Albumin	3.23±0.31	3.2 (2.9-4.4)	3.19±0.28	3.2 (2.9-4.8)	3.182±0.2318	3.2 (2.9-3.9)	3.235±0.2462	3.2 (2.9-4.3)	0.976
ALT	38.93± 10.519	36.00 (25-56)	40.35± 10.281	36 (25-55)	40.50±9.871	40 (26-55)	40.67±10.424	36 (26-55)	0.847
AST	41.13±7.71	44.00 (21-54)	41.7±7.663	44 (21-54)	41.93±7.353	44 (25-54)	42.45±7.550	44 (25-54)	0.710
GGT	34.77±11.194	32 (25-80)	32.32±4.284	31 (28-49)	31.43±3.207	31 (28-39)	31.80±3.602	31 (28-44)	0.116
ALP	106.92±17.712	108 (72-131)	101.45± 17.447	104 (72-129)	101.00±19.075	108 (28-129)	103.97±18.119	109 (72-129)	0.023
TB	1.137±0.2718	1.100 (0.7-1.6)	1.138±0.2457	1.100 (0.7-1.6)	1.130±0.2606	1.2 (0.7-1.6)	1.198±0.2514	1.2 (0.7-1.6)	0.167
AFP	2.943±0.5628	3.1 (1.2-3.4)	2.903±0.6561	3.1 (1.2-3.7)	2.922±0.6181	3 (1.2-3.9)	2.902±0.6074	3 (1.2-4)	0.801
PT	14.1±1.14	14.4 (11.1-16.1)	14.0±0.9441	14.1 (12.2-16.1)	14.0±0.9898	14.1 (12.2-15.2)	13.943±0.9194	13.8 (12.2-15.2)	0.507
Cre	1.052±0.2587	1.100 (0.5-1.6)	1.007±0.2510	1.1 (0.5-1.6)	1.0±0.2123	1.100 (0.5-1.3)	1.040±0.1825	1.1 (0.5-1.3)	0.730

*Friedman test. HCV: Hepatitis C virus, RNA: Ribonucleic acid, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gama glutamyl transferase, ALP: Alkaline phosphatase, TB: Total bilirubin, AFP: Alpha-fetoprotein, PT: Prothrombin time, Cre: Creatinine, SD: Standard deviation, IQR: Interquartile range, max.: Maximum, min.: Minimum

of treatment and at the 12 week follow-up. No mild, moderate, or serious adverse events were observed during or after treatment. All patients were successfully treated.

Discussion

In this study, the results of real-world data on G/P in CHC patients are presented. The SVR rate of G/P in TE/TN CHC patients was 100%, supporting the notion that G/P treatment is effective and tolerable. The high SVR rate with G/P in our study is compatible with many studies that reported the use of G/P for both 8 and 12 weeks of treatment (11,12,13,14,15). Another efficacy and safety study was performed in 102 patients in Korea. G/P therapy proved to be highly effective, with 97.1% of all patients achieving SVR 12, regardless of the presence of CC or the patient's previous CHC treatment experience. Although not statistically significant in this study, there was a difference in the proportion of patients achieving SVR 12 between those receiving 8 weeks of treatment and those receiving 12 or 16 weeks of treatment (98.8% vs. 90.5%, p=0.107). The 12 and 16 week treatment periods consisted of CC and TE patients. The results also showed that liver fibrosis improved after G/P treatment. Pruritus was the most common adverse event (10.8%), followed by fatigue (2.9%), headache (2.0%), and gastrointestinal disturbances (3.9%) were also reported (16). In our study, the fact that viral load was not detected in all patients in the 4th week of treatment indicated that the effectiveness of treatment was high.

In SURVEYOR-I (for genotypes 1, 4, 5 and 6) and SURVEYOR-II (for genotypes 2 and 3), final data from study arms showed an eight-week treatment course of G/P was evaluated in both CC patients and patients with non-cirrhotic genotype 2-6 infection, achieving an overall SVR12 rate of 97% rates were obtained (17). When these data are evaluated although there are no data on reducing the treatment duration, more studies are necessary due to effective responses. In the VOYAGE 1 study, SVR12 was achieved in 352 out of 362 patients with non-cirrhosis who received G/P (97.2%). In VOYAGE-2, 159 out of 160 compensated patients with cirrhosis achieved SVR12 (99%) (18). In EXPEDITION-1, a single-arm, open-label, multicenter phase 3 study, the efficacy and safety of G/P was demonstrated with a 12 week treatment period in TN/TE-CC patients (19). Subsequently, the labeled duration of G/P therapy for TN patients with CC was changed from 12 weeks to 8 weeks for genotypes 1, 2, 4, 5, and 6 in July 2019 and for genotype 3 in March 2020. A highly SVR was achieved with the results of this EXPEDITION-8 study, which led to the addition of 8 weeks of G/P, which is a shorter treatment for CHC in the AASLD and EASL guidelines (3,14). Real-world data demonstrated comparable efficacy of G/P when administered for 8 or 12 weeks in patients with TN/CC CHC (intention-to-treat: 97.4% and 98.1%, respectively) (9,12). Analysis of relevant populations conducted in the same study revealed SVR12 rates of ≥95% regardless of comorbidities. It has been reported in many studies that accompanying diseases and risk factors do not affect SVR (20,21). In our study, comorbidities and substance use, which are the most common risk factors, did not affect the sustained virologic response rates. In addition, the HCV-RNA negativity obtained in all patients at week 4 in our study suggests the possibility of shorter-term treatment with G/P. Today, the leading cause of treatment failure in CHC treatment is medication non-compliance, especially in key populations. Therapeutic strategies with shorter durations are currently being evaluated and may be particularly useful in key populations and in certain settings. Predicting who may respond to short-term treatment with DAAs agents will have important implications for models of care in "hard-to-reach" populations, such as incarcerated patients, people hospitalized with serious injection-related infections, those with psychiatric illnesses, and those with drug-related comorbidities. In the TARGET3D study, which evaluated the effectiveness of 4 weeks of G/P treatment in people with recent (<12 months) HCV infection, the effectiveness was associated with baseline HCV-RNA. In this study, all participants with a baseline HCV-RNA <6.5 log 10 IU/mL achieved SVR (15/15, 100%). Conversely, most participants with baseline HCV-RNA levels >7 log 10 IU/mL (3/5, 60%) experienced virologic failure. The effectiveness of 4 week G/P treatment was lower than that observed with longer treatment durations (≥6 weeks) (22). On the contrary, G/P was found to be highly effective with a 6 week treatment period among people with acute and recent HCV infection (<12 weeks), which is called the hard-to-reach population (77% human immunodeficiency virus positive, 47% substance abusers, and 13% HCV reinfection), in a single-arm, multicenter, international pilot study (22).

Conclusion

Short-acting, pangenotypic DAAs, such as G and P, are increasingly important treatments that can support countries in achieving the WHO goal of eliminating hepatitis C virus (HCV). Our study shows, consistent with real-world evidence, that G/P is a well-tolerated and highly effective pangenotypic treatment for a broad range of HCV-infected patients. Shortening the treatment duration may help address the gaps in care in populations that are difficult to reach and follow.

Ethics

Ethics Committee Approval: This study was approved by the Dicle University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (approval number: 242, date: 13.09.23).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.Y.T., Ç.M., M.K.Ç., Concept: Ç.M., Design: Ç.M., Data Collection or Processing: M.K.Ç., Analysis or Interpretation: A.Y.T., Literature Search: Ç.M., M.K.Ç., Writing: A.Y.T., Ç.M., M.K.Ç.

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

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Research Article

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Access to Treatment of Acute Hepatitis B and Chronic Hepatitis B Acute Exacerbation

Akut Hepatit B ve Kronik Hepatit B Akut Alevlenmede Tedaviye Erişim

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ABSTRACT

Objectives: Acute hepatitis B (AHB) and chronic hepatitis B acute exacerbation (CHBAE) can lead to liver failure, necessitating careful monitoring and urgent intervention. This study aimed to evaluate patients diagnosed with AHB and CHBAE, the antivirals initiated, and the methods of accessing these treatments.

Materials and Methods: This study included patients monitored at our hospital over a 5 year period with diagnoses of AHB and CHBAE. Clinical symptoms of the patients, potential etiologies leading to infection or exacerbation, laboratory values, possible diagnoses, indications for antiviral treatment, methods of treatment access, and disease course were retrospectively evaluated.

Results: Seven patients diagnosed with AHB and 12 with CHBAE were included in the study. Antiviral therapy was initiated in nine patients (47.4%). Among these patients, four began antivirals for coagulopathy, one for pregnancy, one for cessation of previously used antivirals for CHB, and three for ongoing liver function test abnormalities and hepatitis B virus-DNA positivity. Only two patients had swift access to treatment through health insurance coverage, while others pursued alternative routes, such as off-label drug approval. None of the patients developed fulminant hepatitis.

Conclusion: The treatment indications for AHB are clearly established based on the guidelines. Some studies recommend initiating treatment for all CHBAE cases, whereas others suggest treatment only when signs of liver failure are present. Access to treatment for patients who require urgent intervention may be delayed due to non-compliance with healthcare reimbursement

ÖZ

Amaç: Akut hepatit B (AHB) ve kronik hepatit B akut alevlenme (KHBAA) karaciğer yetmezliğine sebep olabilecek, dikkatle izlenmesi ve gerektiğinde acil müdahale edilmesi gereken patolojilerdir. Çalışmamızın amacı AHB ve KHBAA tanılarıyla izlenen hastaları, başlanan tedavileri ve tedaviye erişim yollarını değerlendirmektir.

Gereç ve Yöntemler: Çalışmamıza 5 yıllık süre içinde hastanemizde AHB ve KHBAA tanılarıyla izlenen hastalar dahil edilmiş ve bu hastalara ait bilgiler retrospektif olarak taranmıştır. Hastaların klinik belirtileri, bulaşa veya alevlenmeye sebep olabilecek olası etiyolojileri, laboratuvar değerleri, olası tanıları, antiviral başlanıp başlanmadığı, başlandıysa endikasyonu ve tedaviye ulaşım şekli ile hastalık seyri değerlendirilmiştir.

Bulgular: AHB tanısıyla izlenen yedi (%36,8) ve KHBAA tanısıyla izlenen 12 (%63,8) hasta çalışmaya dahil edilmiş, bu hastaların da dokuzuna (%47,4) antiviral tedavi başlanmıştır. Hastaların dördüne koagülopati, birine gebelik, birine alevlenme öncesi KHB nedeniyle başlanan antivirali kesmiş olması nedeniyle tedavi başlanmış, kalan 3 hastaya ise izlemlerinde devam eden karaciğer fonksiyon testlerindeki anormallik ve hepatit B virüsü-DNA pozitifliği nedeniyle tedavi başlanmıştır. Hastaların yalnızca ikisine geri ödeme kapsamında ilaç raporu çıkarılarak tedaviye hızlıca erişmeleri sağlanmış, diğerleri için endikasyon dışı ilaç onayına başvurmak gibi farklı yollara başvurulmuştur. Hastaların hiçbirinde fulminan hepatit gelişmemiştir.

Sonuç: AHB ve KHBAA karaciğer yetmezliğine sebep olabilecek patolojilerdir. AHB tanısıyla izlenen hastalar için tedavi endikasyonları

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regulations. Adjustments in health insurance coverage for antiviral therapies are necessary to mitigate such delays.

Keywords: Hepatitis B virus, acute hepatitis, acute exacerbation, health insurance, antiviral therapy

rehberler tarafından belirlenmiştir. Çalışmaların bir kısmında KHBAA hastalarının tamamına, bir kısmında ise özellikle karaciğer yetmezliği bulguları olduğunda tedavi başlanması önerilmektedir. Acil tedavi ihtiyacı gelişebilecek bu hastaların tedaviye erişimleri ise sağlık uygulamaları tebliğinin gereklerini karşılamadıkları için gecikebilmektedir. Bu gecikmenin önüne geçebilmek için antiviral tedavilerinin geri ödeme koşullarında düzenlemelerin yapılması gerekmektedir.

Anahtar Kelimeler: Hepatit B virüsü, akut hepatit, akut alevlenme, sağlık sigortası, antiviral

Introduction

Hepatitis B virus (HBV) infection remains one of the leading causes of liver cirrhosis and hepatocellular carcinoma, despite effective vaccines and treatments. It is estimated that 880,000-1.89 million people in the US and more than 250 million people worldwide are infected with HBV. In 2021, 2045 cases of acute hepatitis B (AHB) were reported in the USA, suggesting approximately 13,300 new cases (1). In Turkey, one in every three people is infected with HBV (2).

Patients infected with HBV may present asymptomatically or with no-specific symptoms, such as nausea and vomiting, or with more serious conditions, such as fulminant hepatitis. Although 90% of acute HBV infections in newborns become chronic, this rate is around 5-10% in adults (3). Acute exacerbations are not uncommon in the course of chronic hepatitis B (CHB), with an annual cumulative incidence ranging from 10-30% (4). Immune clearance, spontaneous immune reactivation, discontinuation of nucleos(t)ide analog therapy, use of immunosuppressive therapies, pregnancy, and other conditions can cause exacerbations during the course of CHB. These attacks can be asymptomatic or symptomatic (5,6).

In our country, the criteria for initiating antiviral treatment for CHB are clearly regulated by the Ministry of Health. Treatment recommendations for patients with AHB or CHB acute exacerbation (CHBAE) difficulties in accessing treatment may arise from time to time due to the lack of reimbursement for antiviral treatments in this patient group. The aim of our study was to evaluate the clinical follow-up of patients diagnosed with AHB and CHBAE, the treatments initiated for these patients, and the procurement process of these treatments.

Materials and Methods

Our study included patients followed up with the diagnosis of AHB and acute exacerbations of CHB in of CHB in Recep Tayyip Erdoğan University Training and Research Hospital infectious diseases and clinical microbiology clinic over the past 5 years. Patients with a follow-up duration of >1 year were additionally evaluated to observe the progression of their conditions. Patient age, sex, possible diagnoses, serological test results related to HBV, HBV-DNA levels during follow-up, peak alanine aminotransferase (ALT), bilirubin, international normalized ratio (INR), and the time taken for these values to return to normal ranges were evaluated. Furthermore, if applicable, along with the treatments received, indications, treatment durations, and how these treatments were procured were retrospectively recorded from the hospital data system. Symptoms and signs of patients, potential transmission routes for AHB, such as suspected sexual contact, piercing, surgical operations, invasive procedures, blood transfusions, or conditions that could lead to exacerbations of CHBAE, such as discontinuation of antiviral therapy, pregnancy, use of herbal supplements, or hepatotoxic drug use, were documented based on their medical histories. Additionally, patients were evaluated for the presence of Delta hepatitis or other viral, bacterial, or parasitic infections that could contribute to CHBAE exacerbation.

Acute exacerbation was defined as an abrupt increase in ALT levels to three times the basal level or five times the upper limit of normal (whichever is higher) (7,8).

Chemiluminescent microparticle immunoassay (CMIA) was used for qualitative determination of Hepatitis B-surface antigen (HbsAg), Hepatitis B-e antigen (HBe-Ag) and anti-Hepatitis B-core immunoglobulin M (anti-HBcIgM), immunoglobulin G (anti-HBc IgG), and anti-HBe antibodies. Anti-HBs antibody was quantitatively detected using CMIA. HBV-DNA levels were assessed using real-time polymerase chain reaction.

To determine the possible diagnosis of patients, previous serological test results, high-risk exposure history, serum anti-HBc IgM positivity and titers at the time of diagnosis, anti-HBc IgG positivity and titers, HBV-DNA level, and ALT levels were evaluated.

The decision to initiate antiviral therapy was based on the patient's clinical and laboratory findings, and nucleos(t)ide analog antiviral therapy was initiated for patients with signs of liver failure. If patients' conditions met the criteria of health application regulations for initiating antiviral treatments, drugs were prescribed accordingly. Otherwise, attempts were made to provide drugs by applying for off-label use to the drug-pharmacist association. During this period, medications were procured without prescriptions to avoid delays.

Statistical Analysis

The age was distributed normally, shown as mean ± standard deviation. The distribution of gender, diagnoses, signs and symptoms was presented as percentiles.

Ethical Approval

Ethical approval was obtained from the Ethics Committee of Recep Tayyip Erdoğan University Non-interventional Clinical Research Ethics Committee (approval number: 2024/06, dated: 04.01.2024.)

Results

During the study period, a total of 19 hospitalized patients with diagnoses of AHB and CHBAE were identified in our hospital. The mean age of the patients was 45.3±14.5 years, with 6 (31.6%) women. Seven patients (36.8%) were diagnosed with AHB, while 12 patients (63.2%) were diagnosed with CHBAE. The most common reasons for patient admission were fatigue (63%), loss of appetite (37%), nausea/vomiting (31.5%), jaundice (21%), and high fever (21%). Six patients (31.5%) were asymptomatic, and liver function abnormalities were detected during routine tests. Three of the patients diagnosed with AHB had a history of risky contacts that could lead to transmission, whereas one patient diagnosed with CHBAE was pregnant, one had a COVID-19 infection, and one had exacerbation possibly due to discontinuation of antiviral therapy. Delta virus co/super-infection was not detected in any of the patients (Table 1). All patients included in the study were positive for hepatitis B surface antigen, and anti-HBs positivity was detected in two of them. The highest ALT, INR, total bilirubin, and HBV-DNA levels during the initial follow-up period are presented in Table 2.

Treatment was initiated for one of the AHB patients (14.3%) and eight of the CHBAE patients (66.6%). Four patients were started on antiviral therapy for coagulopathy and one for pregnancy. One of the patients was restarted on antiviral treatment, which he had left voluntarily and was faced with acute exacerbation, and the remaining three patients were initiated on antivirals due to ongoing liver function abnormalities and high DNA levels with the diagnosis of CHB. Four patients with CHBAE did not receive antiviral treatment due to lack of follow-up after discharge and one patient was anti-HBs positive. Among the patients who started treatment, four received disoproxil fumarate, three received alafenamide fumarate, and two received entecavir. Immediate health insurance coverage was provided to only two out of the nine patients who received treatment. One of these patients had previously been

Table 1: Characteristics, risk factors, and signs of patients followed up with a diagnosis of AHB and CHBAE

					Risk factors					Signs				
	Age	Gender	CHB	Possible diagnosis	Discontinuation of antiviral therapy	Pregnancy	Herbal	Hepatotoxic drugs	Other risk factors	Jaundice	Loss of appetite	N/V	Fever	Malaise
Patient 1	63	F	-	AHB	-	-	-	-	-	-	-	-	-	+
Patient 2	62	M	-	AHB	-	-	-	-	CABG	-	-	-	-	-
Patient 3	47	M	+	CHBAE	-	-	-	-	-	-	-	-	-	+
Patient 4	60	M	-	CHBAE	-	-	-	-	-	-	+	+	-	+
Patient 5	46	M	+	CHBAE	+	-	-	+	-	-	-	-	-	-
Patient 6	54	M	+	CHBAE	-	-	-	-	-	-	-	+	+	-
Patient 7	58	M	+	CHBAE	-	-	-	-	-	-	-	-	-	-
Patient 8	24	F	-	CHBAE	-	+	-	-	-	-	-	-	-	-
Patient 9	46	M	+	CHBAE	-	-	-	-	-	-	-	-	-	-
Patient 10	27	M	+	CHBAE	-	-	-	-	-	+	+	-	+	+
Patient 11	23	F	+	CHBAE	-	-	-	-	-	+	+	+	-	+
Patient 12	35	M	+	CHBAE	-	-	-	-	COVID-19	-	-	-	+	+
Patient 13	27	F	+	CHBAE	-	-	-	-	-	-	+	+	-	+
Patient 14	35	M	-	AHB	-	-	-	-	Risky sexual contact	-	-	-	-	+
Patient 15	38	M		CHBAE										
Patient 16	49	M	-	AHB	-	-	-	+	-	+	+	-	+	+
Patient 17	69	M	-	AHB	-	-	-	-	-	+	+	+	-	+
Patient 18	37	F	-	AHB	-	-	-	-	Piercing	-	-	-	-	+
Patient 19	60	F	-	AHB	-	-	-	-	-	-	+	+	-	+

F: Female, M: Male, AHB: Acute hepatitis B, CHBAE: Chronic hepatitis B acute exacerbation, CHB: Chronic hepatitis B, CABG: Coronary artery by-pass great operation, COVID-19: Coronavirus disease 2019; N/V: Nausea/Vomiting

Table 2. Laboratory values of patients and normalization time for abnormal findings

	Possible diagnose	Laboratory Values				Serology						Normalization time (wk)			Seroconversion to anti-HB antibodies	Anti HBs-time (wk)	Viral eradication (wk)
		ALT-max. (IU/mL)	INR-max.	Bilirubin-max. (mg/dL)	HBV-DNA (IU/mL)	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc IgM	Anti-HBc IgG	ALT	INR	Bilirubin			
Patient 1	AHB	1157	0.9	1.5	198200000	+	-	+	+	+	+	12	-	8	+	28	28
Patient 2	AHB	867	1.6	2.0	41937505	+	-	+	-	+	+	16	8	8	+	52	28
Patient 3	CHBAE	2401	1.5	2.5	80778027	+	-	-	+	-	+	6	6	2	-	-	52
Patient 4	CHBAE	1659	1.4	2.4	742	+	+	+	+	+	+	5	1	5	+	0	6
Patient 5	CHBAE	1094	1.1	0.8	6407404	+	-	-	+	-	+	16	-	-	-	-	16
Patient 6	CHBAE	647	1.2	1.1	69424617	+	+	-	+	-	+	12	-	-	+	0	
Patient 7	CHBAE	601	1.2	1.6	1407	+	-	-	+		-	52	-	-	-	-	84*
Patient 8	CHBAE	990	1.2	0.8	83227075	+	-	-	+	-	+	6	-	-	-	-	8
Patient 9	CHBAE	702	1.2	1.0	332130	+	-	-	+		+	76	-	-	-	-	72
Patient 10	CHBAE	1213	1.0	0.5	32431592	+	-	-	+	-	+	8	-	-	-	-	
Patient 11	CHBAE	3279	2.1	9.2	105615	+	-	-	+	+	+	8	1	8	+	14	16
Patient 12	CHBAE	916	1.5	0.6	708	+	-	-	+	-	+	NI	NI	NI	NI	NI	NI
Patient 13	CHBAE	877	1.4	1.4	248700000	+	-	-	+	+	+	NI	NI	NI	NI	NI	NI
Patient 14	AHB	537	0.9	2.2	1201	+	-	-	+	+	+	NI	NI	NI	NI	NI	NI
Patient 15	CHBAE	1145	1.0	1.2	1240000	+	-	-	+	-	+	NI	NI	NI	NI	NI	NI
Patient 16	AHB	3509	1.1	7.2	15650000	+	-	-	+	+	+	8	-	4	-	-	13
Patient 17	AHB	1573	1.2	1.7	51722666	+	-	-	+	+	+	NI	NI	NI	NI	NI	NI
Patient 18	AHB	1559	1.0	3.9	1229545	+	-	-	+	+	+	NI	NI	NI	NI	NI	NI
Patient 19	AHB	1408	1.1	8.5	719400	+	-	-	+	+	+	5	0	6	-	-	NI

*HBV-DNA levels were negative on the third month of antiviral treatment, AHB: Acute hepatitis B, CHBAE: Chronic hepatitis B acute exacerbation, wk: Week, NI: No information, max.: Maximum, ALT: Alanine aminotransferase, IU: Interantional unit, INR: International normalised ratio, HBV-DNA: Hepatitis B virus DNA level, HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, HBeAg: Hepatitis B-e antigen, Anti-HBe: Antibody to hepatitis B-e antigen, Anti-HBc IgM: Immunglobulin M antibody to hepatitis B core antigen, Anti-HBc IgG: Immunglobulin G antibody to hepatitis B core antigen

using antivirals with a diagnosis of CHB, and one was pregnant. Treatment was initiated for the remaining three patients by applying for off-label drug approval, and one patient was started because of a lack of reimbursement coverage (Table 3). None of the patients developed fulminant hepatitis, and there was no need for liver transplantation.

Discussion

Nineteen patients diagnosed with AHB and CHB with CHBAE were included in our study, and antiviral therapy was initiated in nine of them. Only three of these patients were able to access treatment early with health insurance coverage, whereas for others, treatment was attempted through other ways like off-label drug approvals or buying medicines for a fee. Notably, access to antiviral therapy was hindered by the lack of reimbursement coverage for these treatments. Importantly, none of the patients experienced liver failure, transplantation requirement, or death.

AHB and CHBAE are diseases that require careful monitoring and prompt intervention because they are acute pathologies that can lead to liver failure, transplantation, or even death (9). It may be difficult for patients who develop an indication for "urgent" antiviral treatment during the follow-up period to access treatment due to reasons such as the expensiveness of the treatments and the fact that the drugs are not covered by health insurance. Although antiviral indications are determined in the guidelines for these conditions, challenges in accessing treatment due to lack of reimbursement coverage under the current healthcare system regulations can pose significant obstacles.

Although the incidence of symptomatic disease in the acute phase of HBV infection is not high, exacerbations can occasionally occur in the chronic phase due to various reasons. Therefore, a higher incidence of CHBAE was expected among patients presenting to the acute hepatitis clinic (4,5), which was consistent with our study.

Table 3. Treatment indications and treatment access

	Possible diagnose	Indication for treatment	Antiviral treatment	Access to treatment	Special conditions	Treatment duration (wk)
Patient 1	AHB	-	-			-
Patient 2	AHB	Coagulopathy	ENT	OLDA		52
Patient 3	CHBAE	Coagulopathy	ENT	Non-HI	Treatment was started immediately, and health insurance coverage was obtained after liver bx in the 1st month of follow-up	Going on
Patient 4	CHBAE	Coagulopathy	TDF	OLDA	Anti HBs positive HBV-DNA positive	24
Patient 5	CHBAE	CHB	TAF	HI	Exacerbation due to discontinuation of antiviral therapy	Going on
Patient 6	CHBAE	-	-			-
Patient 7	CHBAE	CHB	TAF	HI	Treatment was started after liver biopsy on the 18th month of follow-up	Going on
Patient 8	CHBAE	Pregnancy	TDF	HI	Treatment was stopped after pregnancy	16
Patient 9	CHBAE	CHB	TAF	HI	Treatment was started after liver biopsy in the 10th month of follow-up	Going on
Patient 10	CHBAE	-	-			-
Patient 11	CHBAE	Coagulopathy	TDF	OLDA		24
Patient 12	CHBAE	-	-		Follow-up time is insufficient	
Patient 13	CHBAE	-	-		Follow-up time is insufficient	
Patient 14	AHB	-	-		Follow-up time is insufficient	
Patient 15	CHBAE	CHB	TDF	HI	Treatment was started after liver biopsy in the 3rd month of follow-up, and the follow-up time was insufficient	Unfollowed
Patient 16	AHB	-	-		Follow-up time is insufficient	
Patient 17	AHB	-	-		Follow-up time is insufficient	
Patient 18	AHB	-	-		Follow-up time is insufficient	
Patient 19	AHB	-	-		Follow-up time is insufficient	

AHB: Acute hepatitis B, CHBAE: Chronic hepatitis B acute exacerbation, CHB: Chronic hepatitis B, ENT: Entecavir, TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide fumarate, OLDA: Off-label drug approval, HI: Health insurance, wk: Week, non-HI: Treatment not covered by health insurance, HBV-DNA: Hepatitis B virus DNA level

Among the patients diagnosed with AHB, three had a history of risky contacts, and one underwent coronary artery bypass grafting, potentially indicating postoperative complications or nosocomial exposure. Many of these patients presented with jaundice, a typical clinical manifestation of AHB infection (8). In contrast, patients with CHBAE exhibited a diverse clinical profile and milder symptoms, such as nausea, vomiting, and loss of appetite. Several patients had histories of hepatotoxic drug use, concurrent viral infections, pregnancy, or discontinuation of antiviral drugs, raising the possibility of intensifying chronic liver disease.

Routine antiviral therapy is not recommended for adult patients with AHB, as only 5-10% develop CHB and there is a chance of spontaneous resolution. However, antiviral therapy with nucleos(t)ide analogs is recommended in severe cases with evidence of coagulopathy (INR≥1.5 or prothrombin time prolonged by 4 seconds), prolonged hyperbilirubinemia (elevated bilirubin levels persisting for more than 4 weeks), or signs of hepatic encephalopathy (5,10). In our study, one of the seven patients with AHB received entecavir due to coagulopathy, whereas the others recovered with supportive treatment.

Exacerbations can occur at any stage of chronic HBV infection due to various reasons, such as immunological factors and superinfections, with spontaneous exacerbations being more common, especially in HBeAg negative stage (10-12). Most of the patients included in our study were monitored for CHBAE, and only one tested positive for HBeAg. Due to the risk of decompensation and mortality associated with underlying chronic liver disease, antiviral therapy initiation and continuation are recommended for this patient group (6,9,13). Some studies have emphasized the importance of antiviral therapy, particularly in patients with severe hepatitis causing coagulopathy (8). A significant proportion of patients diagnosed with CHBAE and followed up in our study were started on antiviral therapy.

Among the nine patients included in our study who started antiviral drugs, only two of them were able to access treatment promptly under health insurance reimbursement coverage; other

patients had access through alternative means, leading to delays in early intervention. Despite challenges in treatment access, several patients showed favorable responses to antiviral therapy, as evidenced by seroconversion to anti-HBs and suppression of HBV-DNA levels.

Study Limitations

The limitations of limitations of this study include inadequate follow-up duration for some patients, limited assessment of long-term treatment efficacy and virological response durability, and small number of patients.

Conclusion

Overall, our findings highlight the complex clinical presentation and treatment challenges of patients with AHB and CHBAE. The lack of reimbursement coverage for antiviral therapies under current healthcare regulations in Turkey remains a significant barrier to treatment access and continuity, particularly in emergency situations where immediate treatment initiation is crucial. Updating healthcare regulations is essential to ensure equitable access to essential therapies for hepatitis B management.

Ethics

Ethics Committee Approval: Ethical Approval was obtained from the Recep Tayyip Erdoğan University Non-interventional Clinical Research Ethics Committee (approval number: 2024/06, dated: 04.01.2024.)

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.Ö., T.İ., S.M.Ç., İ.E.Y., U.K., A.E., Concept: A.Ö., T.İ., S.M.Ç., İ.E.Y., U.K., A.E., Design: A.Ö., T.İ., S.M.Ç., İ.E.Y., U.K., A.E., Data Collection or Processing: A.Ö., T.İ., S.M.Ç., Analysis or Interpretation: A.Ö., T.İ., Literature Search: A.Ö., Writing: A.Ö., T.İ., S.M.Ç.

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Hepatitis Delta-Like Viruses

Hepatit Delta-Benzeri Virüsler

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Anahtar Kelimeler: Akut hepatit, hepatit delta virüs enfeksiyonu, HDV-RNA

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Dear Editor;

Hepatitis delta virus (HDV) is a unique defective ribonucleic acid (RNA) virus that requires the helper function of hepatitis B virus (HBV) for its life cycle. HDV-like viruses, also known as HDV-related agents, share similarities with HDV in terms of genomic organization, replication strategy, and pathogenicity. HDV was first discovered in 1977 as a satellite virus requiring the presence of HBV for replication. HDV is classified within the deltavirus genus and is unique in its reliance on HBV for packaging and transmission.

HDV is clearly distinguished from other viroids by its large genome and ability to encode proteins (1).

The origin and evolution of HDV are not fully understood. In recent years, HDV-like viruses that share genetic and functional similarities with HDV have been identified. These HDV-related agents exhibit analogous genomic structures and replication mechanisms, suggesting common evolutionary ancestry (1).

The combination of HDV and HBV infection is considered the most severe form of chronic viral hepatitis because of its more rapid progression toward liver-related death and hepatocellular carcinoma.

This editorial aims to provide a better understanding of HDV-like viruses, their molecular characteristics, epidemiological trends, clinical impact, and innovative therapeutic strategies.

HDV-like viruses possess a circular, single-stranded RNA genome associated with both forms of its only protein (large and small delta antigen or S- and L-HDAg), forming the viral ribonucleoprotein, similar to HDV. The genomic organization typically comprises a viroid-like structure with a single open reading frame encoding viral proteins. The replication strategy of HDV-like viruses involves the utilization of host cellular machinery and relies on the presence of HBV for its life cycle.

HDV is a defective virus and does not code for its own surface proteins; therefore, it uses the three forms of HBV surface proteins (small or S-HBsAg, medium or M-HBsAg and large or L-HBsAg) on which it depends to form its own envelope and egress and re-enter into hepatocytes (2).

During HDV replication in infected cells, two other main forms of viral RNA can be found: the antigenome, which is a replication intermediate and the exact complement of the genome sequence, and the HDV-mRNA coding for the two isoform of HDAg (2).

Worldwide, the number of HDV infections has decreased since the 1980s, mainly because of a successful global HBV vaccination program (3).

Understanding the global prevalence and distribution of HDV-like viruses is essential for assessing their public health impact. Epidemiological studies have revealed the presence of HDV-like agents in various geographical regions, emphasizing the need for continued surveillance and research.

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HDV affects nearly 5% of people who have a chronic infection with HBV.

Globally, the epidemic patterns of HDV infection and its contribution to the burden of liver disease are uncertain. A systematic review estimated that 12 million people worldwide have experienced HDV infection, with a higher prevalence in certain geographic areas and populations. The same evidence suggests that HDV is a significant contributor to HBV-associated liver disease (4).

HDV-like viruses are associated with a spectrum of clinical manifestations, including acute and chronic liver diseases.

HDV infection occurs when people become infected with both hepatitis B and D simultaneously (co-infection) or hepatitis D after first being infected with hepatitis B (super-infection). HDV co-infection with HBV is the most severe form of viral hepatitis, accelerating liver damage and increasing the risk of cirrhosis and liver cancer. Populations that are more likely to have HBV and HDV co-infection include indigenous populations, recipients of hemodialysis and people who inject drugs (3).

Accurate and timely diagnosis of HDV-like infections is crucial for patient management and public health interventions. Major diagnostic and therapeutic innovations have prompted the EASL Governing Board to commission specific Clinical Practice Guidelines on the identification, virologic and clinical characterization, prognostic assessment, and appropriate clinical and therapeutic management of HDV-infected individuals (4).

The unique characteristics of HDV-like viruses pose challenges in developing effective therapeutic interventions.

Hepatitis D infection can be prevented by hepatitis B immunization, but treatment success rates are low.

In cases of positivity, a subsequent step involves using reliable and validated quantitative HDV-RNA assays to confirm active infection. Timely and accurate assessment facilitated by validated serological biomarkers and non-invasive tests is crucial for effective diagnosis and risk stratification. Immunization against HBV is a potent preventive measure. Understanding viral-host-drug dynamics may help develop and optimize response-guided therapies for HDV patients (5,6).

HDV-like viruses, which resemble HDV in terms of genomic organization and replication strategies, represent an intriguing area of research within the virology field. Understanding their molecular characteristics, epidemiology, clinical impact, and therapeutic opportunities is essential for advancing our knowledge and developing targeted interventions against these emerging viral agents.

From a public health perspective and response, we need a better description of the HDV epidemic, standardized testing strategies, and better treatment options (1,4,6).

Addressing the complex challenges of HDV infection requires a multifaceted approach. Raising awareness among healthcare professionals and advocating reflex screening of HBV patients for anti-HDV antibodies is imperative.

Ethics

Authorship Contributions

Concept: M.A., Design: M.A., Y.T.Ç., L.C., Literature Search: M.A., Y.T.Ç., Writing: M.A.

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