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E-ISSN: 2147-2939

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April 2019
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Volume 25

galenos

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Viral Hepatitis Journal

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E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr | **Yayıncı Sertifika No: 14521**
Printing Date: April 2019
E-ISSN: 2147-2939
International scientific journal published quarterly.

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AIM AND SCOPE

Viral Hepatitis Journal (Formerly Viral Hepatit Dergisi) is the regular publishing organ of the Viral Hepatitis Society. This periodical journal covers diagnosis, treatment, epidemiology, prevention and information of hepatitis.

Viral Hepatitis Journal is an open-access journal published 3 times per year (April, August and December). In addition, the special issues are published in some periods. It is a periodic national/international journal, published in English language with abstract and title published also in Turkish language and its editorial policies are based on independent peer-review principles.

The aim of Viral Hepatitis Journal is to continuously publish original research papers of the highest scientific and clinical values specifically on hepatitis, on an international level. Additionally, reviews on basic developments in education, editorial short notes, case reports, original views, letters from a wide range of medical personal containing experiences and comments as well as social subjects are published.

For general practitioners giving first line medical service who are interested in hepatitis, specialists in internal medicine, gastroenterology, microbiology, family physician, public health and hepatology, 'things that must be known' subjects will ensure to involve in Viral Hepatitis Journal.

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Viral Hepatitis Journal is a scientific journal that publishes retrospective, prospective or experimental research articles, review articles, case reports, editorial comment/discussion, letter to the editor, surgical technique, differential diagnosis, medical book reviews, questions-answers and also current issues of medical agenda from all fields of medicine and aims to reach all national/international institutions and individuals.

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Experimental, clinical and drug studies requiring approval by an ethics committee must be submitted to the Viral Hepatitis Journal with an ethics committee approval report confirming that the study was conducted in accordance with international agreements and the Declaration of Helsinki (revised in 2013) (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). The approval of the ethics committee and the fact that informed consent was given by the patients should be indicated in the Materials and Methods section (including approval number). All papers reporting experiments using animals must include a statement in the Material and Methods section giving assurance that all animals have received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (www.nap.edu/catalog/5140.html) and indicating approval by the institutional ethical review board.

The content of the submitted manuscripts should conform to the criteria stated in "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals" published by International Committee of Medical Journal Editors and updated in 2016 (available at http://www.icmje.org/).

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The articles sent to be published in the journal shouldn't have been published anywhere else previously or submitted and accepted to be published. However, a complete report that follows publication of a preliminary report, such as an abstract can be submitted. If authors intend to discard any part of the manuscript, a written application should be sent to the Editor.

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Preparation of research articles and systematic reviews meta-analyses must comply with study design guidelines: CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/),

PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/),

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Authors are encouraged to follow the following principles before submitting their article:

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i. Turkish title, English title, author(s)' name(s) and institution(s) (Turkish and English)
ii. Turkish and English Abstract (max 300 words)
iii. Turkish and English Keywords
iv. Introduction (max 300 words)
v. Materials and Methods (max 400 words)
vi. Results (max 400 words)
vii. Discussion (max 700 words)
viii. Referances (should not exceed 15), all words 2000 not exceed.

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• Articles should be written with double line space in 10 font size and right, left, upper and lower margins should all be 2.5 cm. Writing style should be Arial.

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Abbreviations: Abbreviations should be defined at first mention and used consistently thereafter. Internationally accepted abbreviations should be used; refer to scientific writing guides as necessary.

Cover Letter: Cover letter should include statements about manuscript category designation, single-journal submission affirmation, conflict of interest statement, sources of outside funding, equipments (if so), approval for language for articles in English and approval for statistical analysis for original research articles.

Title Page: Title should be concise and informative (in Turkish and English). The title page should include a list of all contributing authors and all of their affiliations. Positions of authors and names of departments and institutions to which they are attached and the province should be written. Supply full correspondence details for the corresponding author, including phone, mobile phone, fax number and e-mail address.

ARTICLE SECTIONS

The text file should include the title in Turkish, keywords, the title in English, keywords in English, the text of the article, references, tables (only one table for one page) and figure

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legends (if any), respectively. Within the text file, the names of the authors, any information about the institutions, the figures and images should be excluded.

Abstract: Turkish and English abstracts should be given together with the article title. It should be divided into four sections in the following order: Objectives, Materials and Methods, Results and Conclusion. Abstracts should not exceed 250 words. Abstracts for case reports should be unstructured and shorter (average 100-150 words; without structural divisions in Turkish and English).

Objectives: The aim of the study should be clearly stated.

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Results: The detailed results of the study should be given and the statistical significance level should be indicated.

Conclusion: Should summarize the results of the study, the clinical applicability of the results should be defined, and the favorable and unfavorable aspects should be declared.

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• The words should be separated by semicolon (;) from each other.

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• Turkish keywords should be appropriate to "Turkey Science Terms" (www.bilimterimleri.com).

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Materials and Methods: The study plan should be clearly described, indicating whether the study is randomized or not, whether it is retrospective or prospective, the number of trials, the characteristics, and the statistical methods used.

Results: The results of the study should be stated, with tables/figures given in numerical order; the results should be evaluated according to the statistical analysis methods applied. See General Guidelines for details about the preparation of visual material.

Discussion: The study results should be discussed in terms of their favorable and unfavorable aspects and they should be compared with the literature.

Study Limitations: Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion: The conclusion of the study should be highlighted.

Acknowledgements: Any technical or financial support or editorial contributions (statistical analysis, English/Turkish evaluation) towards the study should appear at the end of the article. Only acknowledge persons and institutions who have made substantial contributions to the study, but was not a writer of the paper.

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Case reports should present cases which are rarely seen, feature novelty in diagnosis and treatment, and contribute to our current knowledge. The first page should include the title in Turkish and English, an unstructured summary not exceeding 150 words, and keywords. The main text should consist of introduction, case report, discussion, acknowledgment, conclusion and references. The entire text should not exceed 5 pages (A4, formatted as specified above).

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Review articles can address any aspect of viral hepatitis Review articles must provide critical analyses of contemporary evidence and provide directions of or future research. Most review articles are commissioned, but other review submissions are also welcome. Before sending a review, discussion with the editor is recommended.

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Follow the styles shown in examples below (please give attention to punctuation):

In reference section of the article, there should be no writing in languages other than English. The text language of the article should be indicated in parenthesis at the end of each reference (e.g. Yoldaş O, Bulut A, Altındiş M. The Current Approach of Hepatitis A Infections. Viral Hepatitis J 2012;18:81-86. (Turkish).

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Format for books; initials of author's names and surnames, chapter title, editor's name, book title, edition, city, publisher, date and pages.

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• Article sections

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• Abstract (250 words) (Turkish and English)

• Keywords (minimum 3; maximum 6)

• Article divided into appropriate sections

• Complete and accurate references and citations

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CONTENTS

Research Article

Doi: 10.4274/vhd.galenos.2018.0030
Viral Hepatitis Journal 2019;25(1):1-5

A Comparison of Needle Types and Biopsy Techniques Used in Liver Biopsies of Chronic Hepatitis B Patients

Kronik Hepatit B Hastalarının Karaciğer Biyopsilerinde Kullanılan İğne Tipleri ve Biyopsi Yöntemlerinin Karşılaştırılması

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ABSTRACT

Objectives: To investigate the effect of the biopsy technique used in percutaneous liver biopsies applied with semi-automatic 16 gauge (G) and 18G Tru-cut and Menghini aspiration needles in patients with chronic hepatitis B (CHB) on pathological evaluation.

Materials and Methods: The study included 104 cases diagnosed with CHB who underwent liver biopsy between 2013 and 2018. The pathology results of biopsies were evaluated with the Menghini technique under ultrasound (USG) guidance (n=26), and with 16G (n=54) and 18G (n=24) semi-automatic Tru-cut needles under USG.

Results: The fibrosis score in 5 (9.3%) of the 16G cases and in 3 (12.5%) of the 18G cases, and the ISHAK score in 3 (5.6%) of the 16G and in 1 (4.2%) of the 18G cases could not be determined. There was no significant difference between the methods and needle types in terms of the number of pieces, number of portal sites, fibrosis and ISHAK score (p>0.05). There was a statistically significant difference between the biopsies performed with Menghini method and Tru-cut method with 16G and 18G (p<0.0001) in terms of material length. The diagnosis rates for the Menghini technique, and 16G and 18G Tru-cut needles were 100%, 90.7% and 83.3%, respectively, with no statistically significant difference determined (p>0.05).

Conclusion: Although a larger tissue piece is obtained with the Menghini technique, allowing evaluation of a larger portal area, no significant difference was determined between the techniques in the pathological evaluation. Taking patient safety and comfort into consideration, Tru-cut needle biopsy under USG guidance is recommended rather than the Menghini technique as less trauma is created.

Keywords: Chronic hepatitis B, liver, biopsy, technique, needle

ÖZ

Amaç: Kronik hepatit B (KHB) hastalarında yarı otomatik 16 gauge (G), 18G Tru-cut ve Menghini (aspirasyon) iğneleri ile yapılan perkütan karaciğer biyopsilerinde, kullanılan biyopsi tekniğinin patolojik değerlendirmeye etkisinin araştırılması ve iğne seçiminin tartışılması amaçlanmıştır.

Gereç ve Yöntemler: 2013-2018 yılları arasında KHB tanısı alan ve karaciğer biyopsisi yapılan 104 olgu çalışmaya dahil edildi. Ultrason (USG) ile işaretlenerek yapılan Menghini (aspirasyon) tekniği (n=26), USG eşliğinde 16G (n=54) ve 18G (n=24) yarı otomatik Tru-cut iğne ile yapılan biyopsilerin patoloji sonuçları değerlendirildi. Patoloji değerlendirmesi ISHAK skorlaması ile yapıldı ve fibrozis evresi belirlendi.

Bulgular: Yapılan biyopsilerde 16G ile 5 (%9,3) olguda, 18G ile 3 (%12,5) olguda fibrozis skoru, 16G ile 3 (%5,6) olguda, 18G ile 1 (%4,2) olguda ISHAK skoru belirlenemedi. İğne tipleri ve yöntemler arasında parça sayısı, portal alan sayısı, fibroz ve ISHAK skoru açısından anlamlı fark yoktu (p>0,05). Materyal uzunluğu açısından Menghini yöntemi ile yapılan biyopsiler Tru-cut yöntemi ile kıyaslandığında 16G ve 18G iğneler ile arasında istatistiksel olarak anlamlı fark saptandı (p<0,0001). Alınan materyalin histopatolojik değerlendirmede Menghini tekniği, yarı otomatik 16G ve 18G Tru-cut iğne ile yapılan biyopsilerinde tanı koyulma oranları sırayla %100, %90,7 ve %83,3 bulunmuş olup yöntemler ve iğneler arasında istatistiksel bir fark tespit edilmedi (p>0,05).

Sonuç: Menghini tekniği ile daha büyük doku parçası elde edildiği için diğer tekniğe göre çok daha fazla portal alan değerlendirilebilmektedir. Ancak patolojik değerlendirme açısından yöntemler arasında istatistiksel farklılık saptanmamıştır. Sonuç olarak hasta güvenliği ve konforuda düşünüldüğünde daha fazla travmaya sebep olan Menghini tekniğinden ziyade USG eşliğinde Tru-cut iğne biyopsilerini önermekteyiz.

Anahtar Kelimeler: Kronik hepatit B, karaciğer, biyopsi, teknik, iğne

Karavaş E, Karakeçili F, Balcı MG. A Comparison of Needle Types and Biopsy Techniques Used in Liver Biopsies of Chronic Hepatitis B Patients. 2019;25:1-5.

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Introduction

Liver biopsy has been performed since the end of the 19th century. Paul Ehrlich (Germany) performed liver biopsy for the first time in 1883, and Sheila Sherlock described percutaneous biopsy technique in 1945 (1,2). Menghini performed biopsy with aspiration technique in 1958 (3). The first ultrasound (USG)-guided biopsy was performed in 1972 (4). Today, despite technological advancements in imaging modalities such as USG, computed tomography (CT) and magnetic resonance imaging (MRI), liver biopsy is still recognized as the gold standard method in order to establish the diagnosis, to evaluate the prognosis and to design a treatment plan (5,6).

Major indications for liver biopsy include liver neoplasm, cholestatic liver disease, presence of abnormal hepatic function tests, chronic viral hepatitis, unexplained jaundice, or evaluation of suspicious drug reactions. In addition, liver biopsy is performed to evaluate rejection or to plan treatment in liver transplantation, and to confirm the diagnosis and prognosis in diffuse liver diseases (7,8). Contraindications for liver biopsy are classified into absolute and partial contraindications. Absolute contraindications include non-cooperative patients, severe bleeding disorder (INR >1.6, platelet count <50.000), infection of the hepatic bed, and extrahepatic biliary obstruction, while partial contraindications are abdominal ascites, cyst hydatid, vascular lesions, amyloidosis, and morbid obesity (8,9). The most common complications following liver biopsy are pain and hemorrhage. Pneumothorax, hemothorax, organ perforations, biliary peritonitis, infections, and hemobilia are among the other complications which are rarely seen (8,10).

Liver biopsy is performed using three different methods: percutaneous, transvenous (transjugular, transfemoral) and surgical-laparoscopic biopsy. There are three different methods for percutaneous biopsies as palpation/percussion, radiologic marking, and real time imaging guidance (11,12). Aspiration (Menghini, Jamshidi, Klatskin) needles, manual (Vim-Silverman) or full/semi-automatic Tru-cut needles are used as the biopsy needle (8,11). Technique and needle selection may vary depending on personal experience of the physician, type of approach or biopsy indication.

In this study, we aimed to compare liver biopsy techniques performed in patients with chronic hepatitis B (CHB) and needle selection. Accordingly, we compared USG-guided real time biopsy technique performed with semi-automatic 16 gauge (G) and 18G Tru-cut needles and percutaneous liver biopsy carried out with Menghini (aspiration) needles and investigated the effects of methods used and needle selection on pathologic evaluation.

Materials and Methods

A total of 104 patients diagnosed with CHB and undergone liver biopsy in Erzincan Binali Yıldırım University Medical Faculty between 2013 and 2018 were retrospectively examined and included in the study. This study was approved by Erzincan Binali Yıldırım University Ethics Committee (approval number: 104), and informed consent was obtained from the patients. Coagulation tests were studied in all patients before the biopsy procedure, and biopsy was performed after impaired parameters were improved in patients with a risk for bleeding. The same USG device (GE Logiq P5, Korea, Sangdaewon-don; 1.6-4.5 MHz convex transducer) was used for guidance in all procedures. In biopsies performed with Menghini needle, patients were assessed with USG before the procedure to determine and mark the most appropriate site of biopsy. Similarly, patients were evaluated with USG before the procedure in biopsies performed with Tru-cut needles. The most appropriate position and biopsy site for the patients were determined. None of the patients received sedation. In all patients, the operation site was cleaned with 10% povidone iodine and after waiting for one minute, skin antisepsis was made with 72% alcohol. Local anesthesia (Prilocain, Citanest, AstraZeneca, Germany) was then applied. A small incision was made in the needle entry site. The probe was covered with a sterile sheath in the cases of Tru-cut needles. 18G Menghini (Bard Magnum, Bard Peripheral Vascular Inc. AZ, USA) needles were used in aspiration technique, while 16G 15 cm or 18G 15 cm semi-automatic Tru-cut needles (Geotek Semi-Automatic Biopsy Needle, Ankara, Turkey) were used in the real time application. Biopsy was repeated in the case of a sample length <0.5 cm. The samples were kept in formalin and evaluated by a pathologist experienced in hepatology. ISHAK score, material length, the number of viewed periportal sites, and fibrosis stage were determined for the obtained samples.

We compared and evaluated adequacy of biopsy material for histopathologic evaluation, number of pieces, rate of diagnosis, length of the obtained material, number of portal sites, and rate of complications between the methods and needle types used.

Statistical Analysis

Results of continuous variables were expressed as mean ± standard deviation, and median (minimum-maximum), while categorical variables were given as "n" and percentage (%). Pearson's chi-square and Fisher Exact tests were used for the analysis of categorical variables. Normality of the variables was tested when statistically significant difference between the groups was analyzed. The independent samples t-test was used in comparisons of two independent groups. One way variance analysis was used to compare more than two groups. Bonferroni test was used for post hoc evaluation. A p value of less than 0.05 was considered statistically significant. Data were analyzed using IBM SPSS v.19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows version 19.0 Armong, NY, IBM Corp.) package software.

Results

In our study, 104 patients, who were diagnosed with CHB and underwent liver biopsy, were evaluated. Biopsies performed using the Menghini technique (n=26) by marking with USG and those performed with USG guidance using 16G (n=54) and 18G (n=24) semi-automatic Tru-cut needles were compared. The mean age was 40.16±14.95 (range: 17-78) years. Of all patients, 66 were male and 38 female (Table 1). No statistically significant difference was found between the groups in terms of age and gender (p>0.05).

Biopsy procedure was repeated due to the biopsy material length <5 mm in biopsies performed with 16G (n=1) and 18G (n=1). The mean material length in both methods and procedures performed with three needles was found to be 23.03 mm±8.91

with Menghini needles, 10.15 mm±3.57 with 16G Tru-cut needle, and 12.00 mm±3.35 with 18G Tri-cut needle (Figure 1). There was a statistically significant difference between the biopsies performed with Menghini method and Tru-cut method with 16G (p<0.0001) and 18G (p<0.0001) in terms of material length. No statistically significant difference was found between 16G and 18G needles in biopsies performed with Tru-cut method in terms of material length (p>0.05).

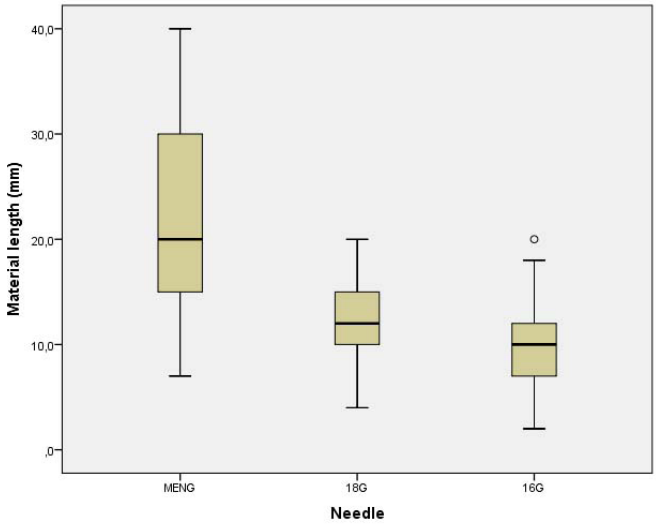

Figure 1. Relationship of material length and needle selection in patients undergone biopsy
MENG: Menghini, G: Gauge

When the number of material pieces was examined; the mean piece number was found to be 1.08±0.27 with Menghini needle, 1.09±0.29 with 16G Tru-cut needle and 1.17±0.38 with 18G Tru-cut needle. No significant difference was found in number of pieces between the methods (p>0.05).

When the number of portal sites of the material taken in the biopsies performed with both methods and three needles were compared; the number of portal sites was found to be ≥6 in all biopsies with Menghini needle, 5.80±0.92 with 16G Tru-cut needle and 5.92±0.88 with 18G Tru-cut needle (Table 2). There was no significant difference in number of portal sites between the methods and needle types (p>0.05).

Fibrosis score (100%) was determined in the histopathologic examination of all biopsy materials obtained with the Menghini method. Fibrosis score could not be determined in 5 (9.3%) patients biopsied with 16G Tru-cut needle and 3 (12.5%) patients biopsied with 18G Tru-cut needle (Table 3). No statistically significant difference was found between the groups in terms of the determination of fibrosis score (p>0.05).

ISHAK score (100%) was determined in the histopathologic examination of all biopsy materials obtained with the Menghini method. Fibrosis score could not be determined in 3 (5.6%) patients biopsied with 16G Tru-cut needle and 1 (4.2%) patient biopsied with 18G Tru-cut needle. No statistically significant difference was

Table 1. Distribution of age and gender in patients undergone biopsy

Needle	Sex		Age				
	Female	Male	n	Mean	SD	Minimum	Maximum
Menghini	11	15	26	40.27	13.75	17	68
18G Tru-cut	9	15	24	36.17	15.58	18	71
16G Tru-cut	18	36	54	41.89	15.15	18	78
Total	38	66	104	40.16	14.95	17	78

G: Gauge, SD: Standard deviation

Table 2. Statistical findings of needle selection and number of portal sites in patients undergone biopsy

Needle	n	Mean	SD	Minimum	Maximum	p
Menghini	26	6.00	0.00	6	6	
16G Tru-cut	54	5.80	0.92	2	8	>0.05
18G Tru-cut	24	5.92	0.88	3	8	
Total	104	5.88	0.78	2	8	

G: Gauge, SD: Standard deviation

Table 3. Needle selection and rate of fibrosis determination in patients undergone biopsy

Needle	Not determined	Determined	Total	p
Menghini	0	26	26	
16G Tru-cut	5	49	54	>0.05
18G Tru-cut	3	21	24	
Total	8	96	104	

G: Gauge

found between the groups in terms of the determination of ISHAK score (p>0.05).

Material sufficient for histopathologic evaluation could be obtained in all patients biopsied with the Menghini technique, with a diagnosis rate of 100%. Whereas, biopsy material was not sufficient for histopathologic evaluation in 7 (8.97%) biopsies performed with 16G and 18G Tru-cut needles and diagnosis could not be established. The rate of diagnosis was found to be 90.7% and 83.3% in liver biopsies performed with semi-automatic 16G and 18G Tru-cut needles, respectively. No statistically significant difference was found between the methods and needles in terms of the rate of diagnosis in histopathologic evaluation with the obtained material (p>0.05).

Discussion

Percutaneous biopsy is a widely used interventional procedure for tissue sampling. Imaging methods are a safe tool in access of the needle to the target (13,14,15). The first preferred method is USG-guided liver biopsy because of its advantages such as evaluation of the parenchyma, imaging of the gallbladder, ability to distinguish intrahepatic main vascular structures with Doppler, not exposing patients to radiation, and being inexpensive, easy to use and portable. In addition, real time imaging is another advantage of USG-guided biopsy (15,16). Percutaneous biopsies using imaging methods have largely prevented complications of blind biopsy and unnecessary operations (10,13). The rate of complications associated with percutaneous liver biopsy is 1%-5% and the rate of mortality is 0.01%-0.009% (17). There are studies reporting that the Menghini and Tru-cut biopsy techniques have no superiority on each other in terms of complications, although there are publications reporting more pain with the Menghini method (18,19,20). Negative pressure created by the nature of the technique in blind biopsies performed with the Menghini method is thought to cause more pain at follow-up after biopsy (21). In our study, none of the patients developed major complication. This was thought to be resulted from small number of our patients and experience of the practitioner. Comparison of complications among the three groups was not included in the study as the number of complications was low.

There are many studies in the literature evaluating liver biopsy-related complications and sufficiency of establishing diagnosis with different techniques and needles of different thickness. However, we could not find a study comparing diagnostic material sufficiency specifically between Menghini and Tru-cut biopsy needle in patients with CHB (6,22,23,24,25).

Quality of liver biopsy is usually determined with length, width, fragmentation, and total number of portal triads and portal routes (26). Quality of a liver biopsy sample plays an important role in evaluation of grade and stage of liver disease in patients with CHB. Length of the material obtained with biopsy is thought to be one of the most important factors in establishing a correct diagnosis (11,23,27). Today, the number of portal triads is thought to be important for a reliable grading and staging. In general, it is accepted that the most appropriate liver biopsy sample must be 20-25 mm in length and must have more than 11 portal triads (28,29). Whereas some studies have reported that materials of 15 mm in length with at least 6-8 portal sites were sufficient for the evaluation (30). In the present study, we considered 6 and more portal triads as sufficient for evaluation.

In our study, material length was statistically significantly longer in the biopsies performed using the Menghini technique compared to those performed with Tru-cut method. However, no significant difference was found in comparisons made for determination of portal sizes, ISHAK scoring or fibrosis.

Although there are studies stating that it is possible to grade CH with 19G and thinner needles, the use of thick cutting needles is recommended in diffuse liver diseases (24,31). Since we considered that the risk of obtaining insufficient tissue with thin needles in biopsies, we preferred 16-18G. In our study, the rates of diagnosis with 16G and 18G needles were 90.7% and 83.3%, respectively, and no statistically significant difference was found between the needles in terms of establishing the diagnosis. However, our rate of diagnosis was lower compared to that in studies in the literature (25,32).

Percutaneous biopsies have become safer and more efficient with innovations in needle designs and technological advancements in imaging modalities (15).

Persons without experience on liver aspiration biopsy are more likely to obtain high-quality samples with fully automatic Tru-cut biopsy needles (15,33,34). Higher-quality tissue samples are obtained with automatic biopsy needles compared to aspiration needles in patients with advanced fibrosis or cirrhosis. Therefore, it has been stated that automatic needles should be preferred in patients with suspected advanced fibrosis or cirrhosis (35).

Study Limitation

Data about biopsy complications were insufficient because of the retrospective design of the study, and relatively lower number of patients compared to the similar studies.

Conclusion

In our study the rates of diagnosis in liver biopsies performed with 16G and 18G Tru-cut biopsies was partially lower compared to the literature. Much more portal sites could be evaluated with Menghini technique compared to the other method since longer tissue pieces were obtained with this technique. Therefore, there was no insufficient sample in biopsies performed with this technique. However, no statistically significant difference was found between this method and the other two methods in terms of pathologic evaluation. Given safety and comfort of the patient, we recommend using USG-guided Tru-cut biopsy rather than the Menghini technique, which causes more trauma.

Ethics

Ethics Committee Approval: This study was approved by Erzincan Binali Yildirim University Ethics Committee (approval number: 104).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., Concept: E.K., Design: E.K., Data Collection or Processing: E.K., F.K., M.G.B., Analysis or Interpretation: E.K., Literature Search: E.K., Writing: E.K., F.K.

Conflict of Interest: The authors declare no conflict of interest.
Financial Disclosure: The authors declare that this study has not received any financial support.

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Research Article

Doi: 10.4274/vhd.galenos.2018.0016
Viral Hepatitis Journal 2019;25(1):6-13

Hepatitis B Virus Infection: Knowledge and Awareness Among the Patients Admitted in a Tertiary Care Hospital in Bangladesh

Hepatit B Virüsü Enfeksiyonu: Bangladeş'te Üçüncü Basamak Hastanesine Başvuran Hastalarda Bilgi ve Farkındalık

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ABSTRACT

Objectives: Hepatitis B virus (HBV) infection is a major cause of morbidity and mortality in Bangladesh. An adequate level of knowledge and awareness among the general population is essential in prevention and control of the infection.
Materials and Methods: A cross-sectional case-control study was conducted among patients who were admitted to our hospital. Data was collected using a self-administered structured questionnaire and analyzed by using SPSS.
Results: Out of 240 respondents included in this study, 120 were hepatitis B surface antigen (HBsAg)-positive and 120, HBsAg-negative. The study shows that as compared to HBsAg-negative counterparts, HBsAg positivity rate was found to be higher in illiterate patients and among farmers, retailers, and day-laborer groups. A significant fraction did not have any knowledge about consequences of hepatitis B infection. More than two-thirds of the patients from both groups were unaware of transmission mode and vaccination of hepatitis B. About one-third (30%) of the respondents mixed up hepatitis A with hepatitis B.
Conclusion: The majority of the patients included in this study had an idea about the cause of HBV infection. However, they had substantial misunderstandings about its mode of transmission and consequences. Hence, a specifically-targeted plan has to be formulated and implemented to increase the awareness about hepatitis B.
Keywords: Knowledge, awareness, admitted patients, hospital, Bangladesh

ÖZ

Amaç: Hepatit B virüsü (HBV), Bangladeş'te morbidite ve mortalitenin önemli nedenlerinden biridir. Genel populasyonda yeterli düzeyde bilgi ve farkındalık, bu enfeksiyonun önlenmesinde ve kontrolünde şarttır.
Gereç ve Yöntemler: Başvuran hastalar arasında kesitsel bir olgu kontrol çalışması yürütüldü. Veriler, kendi kendine yönetilen yapılandırılmış bir anket kullanılarak toplandı ve SPSS kullanılarak analiz edildi.
Bulgular: Bu çalışmaya katılan 240 hastanın 120'si hepatit B yüzey antijeni (HBsAg)-pozitif iken, diğer 120'si negatif idi. Çalışma, HBsAg'nin negatif olduğu meslektaşlarıyla kıyaslandığında, okuma yazma bilmeyen hastalar ile çiftçi, perakendeci ve gündelik işçi grupları arasında HBsAg pozitifliğinin daha yüksek olduğunu göstermiştir. Anlamlı bir kısmın, hepatit B enfeksiyonunun sonuçları hakkında hiçbir bilgisi yoktu. Her iki gruptaki hastaların üçte ikisinden fazlası, bulaşma şeklinden ve hepatit B aşılarından habersizdi. Katılımcıların yaklaşık üçte biri (%30) hepatit A'yı hepatit B ile karıştırmıştır.
Sonuç: Çalışmaya dahil edilen hastaların çoğu HBV enfeksiyonunun nedeni hakkında fikir sahibi idi. Bununla birlikte, bulaşma şekli ve sonuçları hakkında ciddi yanlış anlamaları mevcuttu. Dolayısıyla, hepatit B hakkındaki farkındalığı artırmak için spesifik olarak hedeflenen plan formüle edilmeli ve uygulanmalıdır.
Anahtar Kelimeler: Bilgi, farkındalık, kabul edilen hastalar, hastane, Bangladeş

Zafrin N, Sarkar M.A.S., Rahman Md. M, Salma U, Mahbub T, Azhar M.A. Hepatitis B Virus Infection: Knowledge and Awareness Among the Patients Admitted in a Tertiary Care Hospital in Bangladesh. 2019;25:6-13.

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Introduction

Hepatitis B, a significant global public health issue, can lead to progressive liver damage and liver cancer over time. Globally, more than 240 million people are exposed to chronic liver infections, of whom a million people die each year because of the acute or chronic consequences of hepatitis B (1,2). Besides, nearly one-third of the world population has been suffering from hepatitis B virus (HBV) infection, whereas 350 million of them are infected with chronic hepatitis B characterized by the presence of HBV surface antigen (HBsAg) (3,4).

In Bangladesh, the prevalence rate of HBV infection varies from 2.3% to 9.7% with carriers of 10 million approximately (5,6). HBV is acquired either through vertical transmission, from mother to child, or through horizontal transmission from infected children (7,8), unsafe use of therapeutic injections (9), blood transfusion, and unsafe sexual practices (10). However, because of low HBeAg positivity rate (30.1%) among pregnant females with HBV infection, perinatal or vertical transmission of HBV in Bangladesh is infrequent.

The rate of HBV carriers vary widely among the high-risk population of Bangladesh such as professional blood donors: 19.0 to 29.0%, family members of HBsAg carriers: 20.6%, healthcare workers: 8.7%, parenteral drug abusers: 6.2% to 12.0%, truck drivers: 5.9%, sex workers: 9.7%, and multiple units of blood recipients: 13.8% (11). Besides, HBV infection-a primary reason for liver disease in Bangladesh is responsible from 19.0% to 35.0% of acute viral hepatitis, 35.7% of acute liver failure, 33.3% to 40.5% of chronic hepatitis and 46.8% of hepatocellular carcinoma (12).

Bangladesh being a developing country has less satisfactory health indicators (ranks 142nd of 187 countries on human development index of the United Nations). Over one-third of the total population are living below the poverty line and have a fragile health structure; many patients cannot manage to pay for costly treatment of the diseases caused by HBV infection. Hence prevention is the only safeguard against the epidemic of viral hepatitis. Knowing facts and having proper awareness is critical to prevent the spread of these infections. In Bangladesh, some efforts have been made to assess knowledge and status of hepatitis B vaccination (13) and seroprevalence of hepatitis virus antibodies (14) among newly admitted medical students, the molecular characterization of hepatitis B and C virus infections (15) among the admitted patients, risk factors related to HBsAg reactivity among outdoor patients (16), and knowledge and awareness among the infected male jobseekers to Malaysia (17). However, so far, no study focusing on the knowledge and awareness about hepatitis B transmission and its consequences among both HBV-infected and non-infected patients attending tertiary care hospitals in Bangladesh has been reported. This study is, therefore, designed to assess the level of knowledge and awareness regarding the mode of transmission, consequences, and prevention of HBV infections among patients of different categories admitted to the hospital. Hopefully, the outcomes of this study will render some baseline information necessary for the development of education and communication activities for prevention and management of hepatitis B infection.

Materials and Methods

Methodology

Study Design and Settings

A cross-sectional case-control study was conducted from July 2016 to June 2017 on patients who attended Sir Salimullah Medical College and Mitford Hospital, Clinic of Medicine Inpatient, Dhaka, Bangladesh. The participation in this study was on a voluntary basis. Respondents were selected randomly and were included only after obtaining verbal informed consent. Admitted patients aged 18 years and above who recovered enough to provide a valid response to the questionnaire were included in the study. Respondents with a confirmed diagnosis of HBsAg-positive and no hepatitis B infection were considered as case and control, respectively. It is worth mentioning that data were collected from the patients selected on the first day of their admission. Admitted patients who were affected by other than hepatitis B e.g., chronic obstructive pulmonary disease bronchial asthma, peptic ulcer disease gastroenteritis, cholelithiasis, pancreatitis, poisoning, tuberculosis, urinary tract infection, acute kidney injury, chronic kidney disease, diabetes mellitus with various complications, drug reactions, malignancy, enteric fever, dengue, systemic lupus erythematosus, osteoarthritis, etc. were considered as control. A total of 240 admitted patients were taken as the sample size for this study. This study has been approved by an ethical review committee of the Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh (approval number: ECMD/2016/17).

Statistical Analysis

A self-administered structured questionnaire was used to evaluate knowledge and awareness about the mode of transmission, consequences of and prevention of hepatitis B infection among patients who were admitted to the aforestated hospital. In addition to the demographic data (age, sex, religion, occupation, marital status, educational qualification, monthly income, and residence), 19 questions explored knowledge of hepatitis B and its mode of transmission, 6 questions focused on knowledge about its consequences, 6 questions addressed knowledge on prevention of hepatitis B and 7 questions assessed participants' awareness of HBV infection. The questionnaires were delivered in english and bangla. The survey was conducted in different sessions. The patients were provided with the questionnaire, and a brief explanation was rendered to help them in completing it. Moreover, illiterate patients were interviewed face-to-face with understandable language. Face, content and convergent validity of the questionnaire was executed by expert faculty members of the Sir Salimullah Medical College and Mitford Hospital, Clinic of Inpatient. For reliability, a pilot test with 15 respondents was conducted using the preliminary questionnaire, and internal consistency (Cronbach's coefficient, α=0.77) was found to be in acceptable ranges (18). After data collection, demographic characteristics of the respondents were analyzed using descriptive statistics. Answers to knowledge items with response options of yes, no, and not sure/don't know were divided into yes versus other if the right answer was yes (e.g., sexual intercourse can spread hepatitis B), and no versus other if the right answer was no (e.g., hepatitis B can be spread through coughing). A composite

knowledge score was also created by summing the number of correct answers to the items addressing hepatitis B transmission. While responding to a Likert questionnaire item, respondents stipulated their level of agreement to a statement. SPSS 17.0 was utilized to analyze and process the data. The test statistics used for data analysis were student's t-test and chi-square test. A p value of ≤0.05 was considered statistically significant.

Results

Demographic Characteristics

A total of 240 respondents were included in this study. Among them, 120 were HBsAg-positive (case group) and the other 120 were HBsAg-negative (control group). Table 1 demonstrates the demographic profile of the respondents. From the table, it is evident that the number of patients from the most common age groups, i.e., 31-40 years, 41-50 years, and more than 50 years were higher in the case group in comparison with the control group and the mean ± standard deviation (SD) age of the case and the control groups were 42.5±12.3 years and 37.8±14.6, years respectively. Over three quarters (77.1%) of the case group were male; whereas males constituded 45.7% of the control group. However, the number of females was higher in the control group (54.3%) than that in the case group (22.9%). Educational status describes that about 37% of the case group was primary level educated, 8.6% secondary, 12.9% higher secondary, 4.3% graduate and 2.9% was postgraduate. In control group, 15.7% had education up to primary level, 21.4% secondary, 27.1% higher secondary, and 18.6% graduate. A higher frequency of HBsAg-positivity was found in illiterate patients as compared to HBsAg-negative counterparts (34.3% vs 17.1%, p<0.001). Occupation-wise, a larger proportion of farmers, retailers, and day-laborer was found in the case group than those in control group; while housewives, service holders, and students were found more in the control group than those in the case group. Besides, the frequency of HBsAg-positivity was found greater in the respondents from the farmers, retailers and day-laborers as compared to HBsAg-negative counterparts (18.6% vs 5.7%; 34.3 vs 14.3; and 7.2 vs 1.4; p<0.001). The majority (90%) of the respondents in control group was Muslim, 8.6% Hindu and the remaining 1.4% was Christian. Conversely, all of the case group respondents were Muslim. Married participants were equally distributed (80%) in the case and the control groups. However, over 14% of case group was unmarried and 5.7% widow; whereas 17.1% of the control group was unmarried and 2.9% widow. Over 47% of patients in case group was rural residents, 48.6% urban and a very few (4.3%) was slum residents. On the other hand, 34.3% of the control group came from rural regions and the rest 65.7% was from urban areas.

Clinical and Behavior of the Respondents

Table 2 describing the clinical characteristics of the respondents reveals that all of the variables like jaundice (75.7% vs 7.4%, p<0.001), history of sexually transmitted disease (18.6% vs 2.9%, p=0.003), history of blood transfusion (18.6% vs 1.5%, p<0.001), intra venous drug abuse (5.7% vs 1.5%, p<0.001), and regular consumption of alcohol (25.7% vs 1.5%, p<0.001) were significantly higher in case group than in the control group.

Assessment of Knowledge of Hepatitis B

A total of 38 questions were used to assess the knowledge and the awareness of the admitted patients about hepatitis B. Score "1" was given for each correct response and "0" for each wrong response. The score obtained for each discrete question were then added together to find an integrated score out of 38. The total score thus obtained from the respondents' answers was converted into percentage and was subdivided into 5 categories indicating highly dissatisfactory (0-20%), dissatisfactory (21-40%), neither satisfactory nor dissatisfactory (41-60%), satisfactory (61-80%), and highly satisfactory (>80%). As shown in the Table 3, neither satisfactory nor dissatisfactory as well as satisfactory level of knowledge was noticed to be considerably higher in the case group as compared to the control group (41.4% vs 34.3% and 24.2% vs 14.3%, respectively). In contrast, highly dissatisfactory and dissatisfactory level of knowledge was found higher in the control group than in the case group (27.2% vs 14.3% and 24.2% vs 20.1%, respectively). However, the association between the groups concerning the level of knowledge and awareness were not statistically significant (p=0.494).

Again, Tables 4,5,6 illustrate the level of knowledge regarding hepatitis B and mode of transmission, consequences and prevention of HBV infections among the respondents of two different groups. After evaluating the respondents' opinion, it was found that the HBsAg-positive respondents correctly answered more questions (29 questions out of 38) in comparison with the HBsAg-negative patients.

From the Table 4 demonstrating the knowledge about hepatitis B and its mode of transmission, it is found that 75.7% of the HBsAg-positive respondents realized hepatitis B as a significant health problem in Bangladesh. 84.3% and 65.7% of the interviewees of the case and the control groups respectively identified it as an infectious disease; whereas only 52.9% and 28.6% of the respective groups adequately respond that virus was a cause of hepatitis B infection. When the respondents were questioned about the organs affected by HBV infection, respectively 74.3% and 80% of the case and the control groups correctly answered as liver, while 25.7% and 20% give an incorrect answer. Moreover, regarding mode of transmission of hepatitis B, 50% and 70% of the case and control groups respectively mentioned blood and blood products transfusion, 50% and 62.9% infected needles, 35.7% and 27.1% unsterilized surgical/dental instruments, 21.4% and 25.7% "from mother to baby" and only 47.1% and 52.9% referred to sexual intercourse.

Table 5 shows the various level of knowledge about the consequences of HBV infection among the patients of two different groups. From the table, it is clear that the case group had higher level of knowledge about the consequences of hepatitis B infection than the control group: development of cirrhosis (40% vs 24.3%, p=0.016), liver cancer (48.6% vs 31.4%, p=0.038), blood vomiting or black stool (37.1% vs 31.4%, p=0.476), recurrent abdominal and leg swelling (42.9% vs 17.1%, p=0.001), drowsiness or unconsciousness (31.4% vs 11.4%, p=0.004). However, in both groups, a few percentages of the patients were found to have knowledge that HBsAg-positive patients remain carrier. Moreover, the results above indicate the fact that a significant fraction of both groups do not have adequate knowledge about the consequences of the hepatitis B infection.

Table 1. Frequency distribution of different demographic variables

Age group	Group		p
	Case (n=120)	Control (n=120)	
≤20	7 (5.7)	14 (10.0)	0.040
21-30	15 (12.9)	42 (30.0)	
31-40	27 (22.9)	26 (18.6)	
41-50	45 (37.1)	34 (24.3)	
>50	26 (21.4)	24 (17.1)	
Mean ± SD	42.5±12.3	37.8±14.6	
Educational status			
Illiterate	41 (34.3)	21 (17.1)	<0.001
Primary	46 (37.1)	19 (15.7)	
Secondary	10 (8.6)	26 (21.4)	
Higher secondary	15 (12.9)	32 (27.1)	
Graduate	5 (4.3)	22 (18.6)	
Post graduate	3 (2.9)	0	
Occupation			
Farmer	22 (18.6)	7 (5.7)	<0.001
Retailer	41 (34.3)	17 (14.3)	
Housewife	21 (17.1)	31 (25.7)	
Day laborer	9 (7.2)	2 (1.4)	
Service	25 (21.4)	44 (37.1)	
Student	2 (1.4)	19 (15.7)	
Monthly income			
<5000	56 (46.4)	32 (26.7)	0.005
5000-10000	35 (29.0)	19 (15.6)	
10000-20000	17 (14.5)	42 (35.6)	
>20000	12 (10.1)	27 (22.2)	
Sex group			
Male	108 (77.1)	55 (45.7)	<0.001
Female	32 (22.9)	65 (54.3)	
Religion			
Muslim	120 (100)	108 (90)	0.047
Hindu	00	10 (8.6)	
Christian	00	2 (1.4)	
Marital status			
Married	96 (80.0)	96 (80.0)	0.005
Unmarried	17 (14.3)	21 (17.1)	
Widows	7 (5.7)	3 (2.9)	
Residence			
Rural	57 (47.1)	41 (34.3)	0.035
Urban	58 (48.6)	79 (65.7)	
Slum	5 (4.3)	0	

Figures in the parenthesis denote the corresponding (%); χ^2 test was employed to analyze the data
SD: Standard deviation

Table 6 displays a various level of knowledge regarding suggestive prevention and treatment of HBV among the patients of two different (case and control) groups. From the table, it is evident that only a small fraction of the patients from both groups knew that treatment for hepatitis B was available. Their level of knowledge about curability of hepatitis B was found to be quite

Table 2. Information about clinical and behavior of respondents

Information	Group		p
	Case (n=120)	Control (n=120)	
Jaundice	91 (75.7)	9 (7.4)	<0.001
History of STD	22 (18.6)	3 (2.9)	0.003
H/O blood transfusion	22 (18.6)	2 (1.5)	<0.001
Intra venous drug abuse	7 (5.7)	2 (1.5)	<0.001
Alcohol consumption	31 (25.7)	2 (1.5)	<0.001

Figures in the parenthesis denote the corresponding (%); $\chi 2$ test was employed to analyze the data
STD: Sexually transmitted disease

Table 3. Patients' knowledge and awareness measured on Likert scale between groups

Clinical variables	Group		p
	Case (n=120)	Control (n=120)	
Highly dissatisfactory (≤20%)	17 (14.3)	33 (27.2)	0.494
Dissatisfactory (21-40%)	24 (20.1)	29 (24.2)	
Neither satisfactory nor dissatisfactory (41-60%)	50 (41.4)	41 (34.3)	
Satisfactory (61-80%)	29 (24.2)	17 (14.3)	
Highly satisfactory (>80%)	0	0	

Figures in the parenthesis denote the corresponding (%); $\chi 2$ test was employed to analyze the data

Table 4. Knowledge about hepatitis B and its mode of transmission

Questions asked to respondents		Respondents' opinion		p
		Case (n=120)	Control (n=120)	
Q1.	Is it a major health problem in Bangladesh?	91 (75.7)	9 (7.4)	<0.001
Q2.	Is hepatitis B infectious?	101 (84.3)	79 (65.7)	0.024
Q3.	Does the virus cause hepatitis B?	63 (52.9)	34 (28.6)	0.014
Q4.	Which organ of the body is affected?	-	-	-
-	Liver	89 (74.3)	96 (80.0)	0.631
	Heart	26 (21.4)	9 (7.1)	0.017
Q5.	Is it a genetic disease (heredity)?	14 (11.4)	5 (4.3)	0.116
Q6.	Is it airborne (coughing or sharing a room)?	14 (11.4)	3 (2.9)	0.049
Q7.	Is it transmitted from mother to baby?	26 (21.4)	31 (25.7)	0.550
Q8.	Is it transmitted from one person to other?	55 (45.7)	79 (65.7)	0.017
Q9.	Is it transmitted by sharing food?	22 (18.6)	12 (10.0)	0.147
Q10.	Is it transmitted by touching/handshaking?	19 (15.7)	7 (5.7)	0.264
Q11.	Is it transmitted by sharing razors?	48 (40.0)	21 (17.1)	0.003
Q12.	Is it transmitted by piercing/tattooing?	22 (18.6)	15 (12.9)	0.353
Q13.	Is it transmitted by sharing utensils?	34 (28.6)	7 (5.7)	<0.001
Q14.	Is it transmitted through contaminated food?	36 (30.0)	12 (10.0)	0.003
Q15.	Is it transmitted through blood and blood products?	60 (50.0)	84 (70.0)	0.016
Q16.	Is it transmitted through reuse of infected needles?	60 (50.0)	75 (62.9)	0.125
Q17.	Is it transmitted through sexual intercourse?	57 (47.1)	63 (52.9)	0.499
Q18.	Is it transmitted through unsterilized surgical/dental instruments?	43 (35.7)	33 (27.1)	0.275
Q19.	Is it transmitted through saliva?	24 (20.0)	21 (17.1)	0.664

similar and inadequate (20% vs 10%, p=0.098). However, the majority of the patients of both groups knew about the availability of its vaccine. Control group was found to have higher knowledge about the place of getting the vaccine than the case group (47.1% vs 65.7%, p=0.027). More patients from control group than the case group correctly answered that HBV infection could be prevented by avoiding abnormal sexual behavior (45.7% vs 65.7%, p=0.017). However, opposite scenario was observed when they were asked whether the risk of HBV infection could be avoided by using a condom (30% vs 17.1%, p=0.073) or not.

Assessment of Awareness About Hepatitis B

As shown in Table 7, awareness of hepatitis B was evaluated by asking seven questions. The result shows that more than two-thirds of the admitted patients from both groups were not aware of transmission mode and hepatitis B vaccination. Compared to case group, more patients from the control group agreed that everyone should ask for blood screening before transfusion (42.9% vs 67.1%, p=0.004), screen the blood if female/male is HB carrier (37.1% vs 52.9%, p=0.062) and get vaccinated against hepatitis B (60% vs 65.7%, p=0.484). Irrespective of the groups they belong, a small fraction of the respondents thought that HBsAg-positive patients could donate blood. On the other hand, more than 90% of the patients from each group agreed on the point that infected patients do not need further investigation and treatment to avoid complications of HBV. Interestingly, more than one-fourth of the study participants from both groups responded that unqualified traditional practitioners can cure HBV.

Table 5. Knowledge about consequences of hepatitis B infections

	Questions asked to respondents	Respondents' opinion		p
		Case (n=120)	Control (n=120)	
Q20.	Does HBsAg-positive patient remain as a carrier?	17 (14.3)	3 (2.9)	0.016
Q21.	Can HBV-infected patient develop cirrhosis?	48 (40.0)	29 (24.3)	0.047
Q22.	Can HBV-infected patient develop liver cancer?	58 (48.6)	38 (31.4)	0.038
Q23.	Can HBV-infected patient develop blood vomiting or black stool?	45 (37.1)	38 (31.4)	0.476
Q24.	Can HBV-infected patient develop recurrent abdominal and leg swelling?	51 (42.9)	21 (17.1)	0.001
Q25.	Can HBV-infected patient develop drowsiness / unconsciousness?	38 (31.4)	14 (11.4)	0.004

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

Table 6. Knowledge about prevention of hepatitis B

	Questions asked to respondents	Respondents' opinion		p
		Case (n=120)	Control (n=120)	
Q26.	Is treatment available?	24 (20.0)	12 (10.0)	0.098
Q27.	Is vaccine available?	72 (60.0)	101 (84.3)	0.001
Q28.	Do you know where you can get the vaccine?	57 (47.1)	79 (65.7)	0.027
Q29.	Is hepatitis B curable?	24 (20.0)	12 (10.0)	0.098
Q30.	Does avoiding abnormal sexual behavior protect from hepatitis B?	55 (45.7)	79 (65.7)	0.017
Q31.	Does using a condom avoid the risk of hepatitis B	36 (30.0)	21 (17.1)	0.073

Table 7. Respondents' awareness about hepatitis B

	Respondents' agreement with the following statements	Respondents' opinion		p
		Case (n=120)	Control (n=120)	
Q32.	Ask for the screening of blood before transfusion	51 (42.9)	81 (67.1)	0.004
Q33.	F/M hepatitis B carriers should screen for hepatitis B	45 (37.1)	63 (52.9)	0.062
Q34.	HBV-infected patients should go for further investigation and treatment to prevent complications of HBV	12 (10.0)	9 (7.1)	0.546
Q35.	Everyone should get vaccinated against hepatitis B	72 (60.0)	79 (65.7)	0.484
Q36.	HBsAg-positive patients need vaccination	17 (14.3)	7 (5.7)	0.091
Q37.	HBsAg-positive patients can donate blood	7 (5.7)	3 (2.9)	0.989
Q38.	Unqualified traditional practitioners can cure HBV	29 (24.3)	38 (31.4)	0.346

F: Female, M: Male, HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen

Discussion

In this study, the frequency of HBsAg-positivity was found to be higher in illiterate patients compared to HBsAg-negative counterpart indicating the fact that awareness of mode of transmission was related to education level and needs to be built in a less educated segment of the society. Farmers, retailers and day laborers are more commonly affected by HBV infection as compared to HBsAg-negative patients. It shows that hepatitis B has an impact on the patients belonging to a diversity of business from low to high income. Moreover, nearly half (46.4%) of HBsAg-positive patients are from the lowest income-segment under consideration. These results were similar to that previously reported (19,20,21). The higher prevalence of HBV infection can, therefore, be attributable to the lack of education, poverty and low socio-economic status of the individuals.

Among the hepatitis B affected patients, the prevalence of HBsAg-positivity was found to be higher in urban-based population (48.6%) than the rural-based population and significantly higher among males (77.1%) than females which is quite similar to the results reported by Lingao et al. (22). This prevalence of HBsAg-positivity is because the urban male population is more exposed to the HBsAg risk factors probably due to their inherently more active lifestyle or behavior. Besides, it is observed from the study that the prevalence of HBsAg was significantly higher among married (80%) than single patients. However, Comia et al. (23) in their study showed no significant difference between infected married and single cases. Although with no clear evidence at hand, it is possible that these infected married individuals may have multiple risk factors for infection.

HBV infection, an emerging global health problem, is a common infection in Bangladesh. This study shows that knowledge and awareness of hepatitis B infection and its consequences among patients admitted to SSMCH are variable. Majority mentioned that hepatitis B was an infectious disease caused by a virus and could affect the liver. Respondents, on the other hand, were found to have imperfect knowledge about the specific consequences of this disease and its preventive measures, i.e., their overall level of knowledge and awareness about hepatitis B was not satisfactory (level of dissatisfaction was found to be 51.4%). Perhaps, this is because the majority of our respondents were least educated and from low-income group. Thus, the knowledge and the awareness need to be strengthened more in the least educated and low-income segments of the society.

This study also discovers gaps in public knowledge about the mode of transmission of HBV. Specifically, less than a half of the HBsAg-positive patients recognized that sexual contact (47.1%). Sharing a razor (40%). using unsterilized surgical/dental equipment (35.7%), sharing food (18.6%), and sharing utensils could spread the virus. Half (50%) of them identified "unsafe blood and blood product transfusion" and reuse of injected needles as major causal factors. Besides, 21.4% and 45.7% of respondents of this group thought that hepatitis B could spread from "mother to baby through childbirth" and "one person to another" respectively. However, about one-third (30%) of the respondents mixed up hepatitis A with hepatitis B, and mistakenly mentioned that eating contaminated food was a mode of transmission for hepatitis B. Despite knowing the availability of vaccine, only one-fifth of the respondents believed that hepatitis B was treatable and curable. The similar results are also found in previous studies (24,25,26) conducted by various research groups.

From the above discussion, it is apparent that though the majority of the patients admitted to this hospital had an idea about the cause of HBV infection, they had substantial misunderstandings about its mode of transmission and consequences. Moreover, they took its preventive measures too lightly. These observations were found quite similar to those of Choe et al. (27).

Conclusion

Admitted patients (both HBV infected and non-infected) from least educated and a low-income segment of the society and the urban male populations were more exposed to the HBsAg risk factors. They were found to have an inadequate overall level of knowledge and awareness about HBV infection and its consequences. They had a considerable misapprehension about its mode of transmission. Therefore, large-scale studies are needed to formulate a plan for educating the patients regarding the mode of transmission and the fate of HBV infection. The knowledge gap derived from this study is to be addressed adequately through proper health education to create awareness and hence, prevent HBV infection. An effective health promotion program encouraging the urban male population to change their risky behaviors need to be developed and implemented, and specifically-targeted hepatitis B awareness-raising campaigns need to be launched for general as well as high-risk populations at healthcare setting and community level.

Ethics

Ethics Committee Approval: This study has been approved by an ethical review committee of the Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh (approval number: ECMD/2016/17).

Informed Consent: Respondents were selected randomly and were included only after obtaining verbal informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Design: N.Z., U.S., Data Collection or Processing: N.Z., M.A.S.S., T.M., Analysis or Interpretation: N.Z., Literature Search: M.A.A., Md.M.R., Writing: N.Z.

Conflict of Interest: The authors claim that they have no conflict of interest.

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

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Research Article

Doi: 10.4274/vhd.galenos.2018-0018
Viral Hepatitis Journal 2019;25(1):14-18

Frequency of Hepatitis Delta Virus in Hepatitis B Surface-antigen-positive Patients

Hepatit B Yüzey Antijeni-pozitif Hastalarda Hepatit Delta Virüsünün Sıklığı

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ABSTRACT

Objectives: The prevalence of hepatitis delta virus (HDV) worldwide shows geographical differences. Although there are several studies on anti-HDV seroprevalence rates in hepatitis B surface antigen (HBsAg)-positive patients in Turkey, studies on HDV-RNA prevalence in this patient population are limited. It was aimed to detect the frequency of anti-HDV antibodies and HDV-RNA in HBsAg-positive patients in this study.

Materials and Methods: This retrospective study included 2089 HBsAg-positive patients in whom anti-HDV was analyzed between April 2015 and March 2017. Anti-HDV test was performed in serum samples obtained from HBsAg-positive patients by enzyme-linked immunosorbent assay. In anti-HDV-positive patients, HDV-RNA was analyzed in serum samples by real-time polymerase chain reaction.

Results: The seroprevalence of anti-HDV was 4.1% (85/2089), while the rate of HDV-RNA positivity was 2.4% (51/2089). HDV-RNA was detected in 60% (51/85) of anti-HDV-positive patients. The frequency of anti-HDV and HDV-RNA was highest in the 50-59 age group.

Conclusion: The frequency of HDV in this study was found to be consistent with regional data. HDV viremia was detected in only 60% (51/85) of the anti-HDV-positive patients. Since anti-HDV antibodies may remain after recovery, it is important to investigate HDV-RNA to determine the true prevalence of HDV.

Keywords: Hepatitis delta virus, anti-HDV, HDV-RNA, HBV

ÖZ

Amaç: Dünya genelinde hepatit delta virüsünün (HDV) yaygınlığı coğrafi farklılıklar göstermektedir. Her ne kadar Türkiye'de hepatit B yüzey antijeni (HBsAg) pozitif olan hastalarda anti-HDV seroprevalans oranları konusunda birçok çalışma olmasına rağmen, bu hasta popülasyonunda HDV-RNA prevalansı ile ilgili çalışmalar sınırlıdır. Bu çalışmada HBsAg pozitif olan hastalarda anti-HDV antikorları ve HDV-RNA sıklığının saptanması amaçlandı.

Gereç ve Yöntemler: Bu retrospektif çalışma, Nisan 2015 ve Mart 2017 tarihleri arasında HBsAg-pozitif hastalarda anti-HDV testi çalışılan 2089 hastayı kapsadı. HBsAg-pozitif hastalardan alınan serum örneklerinde anti-HDV testi, enzim bağlı immünosorbent metod kullanılarak yapıldı. Anti-HDV-pozitif hastalarda, HDV-RNA, gerçek zamanlı polimeraz zincir reaksiyonu ile serum örneklerinde analiz edildi.

Bulgular: Anti-HDV seroprevalansı %4,1 (85/2089) iken HDV-RNA oranı %2,4 (51/2089) idi. HDV-RNA, anti-HDV pozitif olan hastaların %60'ında (51/85) tespit edildi. Anti-HDV ve HDV-RNA sıklığı 50-59 yaş grubunda en yüksekti.

Sonuç: Bu çalışmada HDV sıklığı bölgesel verilerle tutarlı bulundu. HDV viremisi, anti-HDV pozitif olan hastaların sadece %60'ında (51/85) tespit edildi. Anti-HDV antikorları iyileşmeden sonra da pozitif kalabileceğinden dolayı, HDV'nin gerçek prevalansını belirlemek için HDV-RNA'nın araştırılması önemlidir.

Anahtar Kelimeler: Hepatit delta virüs, anti-HDV, HDV-RNA, HBV

Yolcu A, Karabulut N, Alaçam S, Önel M, Büyük M, Güllüoğlu M, Ağaçfidan A. Frequency of Hepatitis Delta Virus in Hepatitis B Surface-antigen-positive Patients. 2019;25:14-18.

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Introduction

Hepatitis delta virus (HDV), only affects patients with hepatitis B virus (HBV) infection, is a defective hepatotropic virus, as it requires hepatitis B surface antigen (HBsAg) to gain entry into the cell (1). HDV, first discovered in 1977 by Mario Rizetto, is RNA virus with a negative polarity single-stranded circular genome (2). According to the International Committee on Taxonomy of Viruses, HDV is classified in the genus delta virus (3).

The routes of transmission of HDV are similar to those of HBV. It can be transmitted via blood transfusion, intravenous drug use, sexual contact, sharing personal care items, and nosocomial routes. It has been reported that this infection can be transmitted among family members in countries with a high viral prevalence. In addition, intravenous drug use is important in the transmission of HDV in Northern Europe and in countries where HDV prevalence is low (4,5). Globally, countries are classified for asymptomatic HBV carriers as very low endemicity areas for HDV rates of 0-2%, low for 3-9%, medium for 10-19%, and high endemic areas for >20%; while in chronic HBV-infected patients, it is classified as for <1%, 3-9%, 30-60%, and >60%, respectively. Turkey is considered a medium endemic area for HDV infection with regional differences (6,7).

HDV infection occurs always in association with hepatitis B infection because of HBV dependence of HDV. The clinical course of HDV infection varies from acute self-limiting infections to fulminant hepatitis. Chronic liver infection can cause end-stage liver disease-related complications such as rapid progression of fibrosis, hepatic decompensation, and hepatocellular carcinoma (1). Simultaneous occurrence of HBV and HDV infections is considered coinfection, while the subsequent HDV infection in a HBsAg-positive person is named as superinfection (8). Chronicity rate in coinfection and superinfection is 2-20% and 90%, respectively (9).

Detection of anti-HDV total, immunoglobulin (Ig) G or IgM antibodies in serum or plasma, HDV antigen in serum, liver biopsy and molecular methods are used for the diagnosis of HDV infection. Anti-HDV positivity does not always reflect the presence of active HDV infection. Detection of HDV-RNA is the most sensitive method for assessing active HDV infection (10).

Studies on HDV-RNA are limited, while there are many anti-HDV seroprevalence studies in HBsAg-positive patients in Turkey. Thus, it was aimed to detect the frequency of anti-HDV and HDV-RNA in HBsAg-positive patients in a reference university hospital in Istanbul, Turkey.

Materials and Methods

This retrospective study included 2089 HBsAg-positive patients who were analyzed for anti-HDV between April 2015 and March 2017 at the Istanbul University, Istanbul Faculty of Medicine, Department of Medical Microbiology, Division of Virology and Fundamental Immunology, Istanbul, Turkey. This study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (approval number: 2017/651/11). This study was carried out in accordance with the principles of the Helsinki Declaration.

Anti-HDV and HBsAg tests were studied in serum samples using micro-ELISA kits (Dia. Pro, Diagnostic Bioprobes, Milano, Italy) on a Triturus analyzer (Grifols, Parets del Valles, Spain). The positive and negative control samples were included in each run. Extraction of HDV-RNA was performed using a High Pure Viral Nucleic Acid Kit (Roche Applied Science, Basel, Switzerland) or EZ1 virus mini kit V2 (Qiagen, Germany). Extraction of HBV-DNA was performed using the QIAamp DNA Blood Mini Kit (Qiagen, Germany) according to the manufacturer's recommendations. HDV-RNA is firstly transcribed into cDNA using the transcriptor first strand cDNA synthesis V6 kit (Roche Diagnostics, Mannheim, Germany), and then cDNA was amplified on LightCycler 2.0 real-time polymerase chain reaction (PCR) (Roche Diagnostics GmbH, Switzerland) or Rotor-Gene Q (Qiagen, Germany). HBV-DNA was amplified by real-time PCR on Rotor-Gene Q (Qiagen, Germany).

Biopsy results of only 37 anti-HDV-positive patients could be included in this study between April 2015 and March 2017. The histological activity index and fibrosis were assessed by the modified Knodell scoring system.

Statistical Analysis

SPSS 21 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The suitability of the variables to the normal distribution was examined via visual methods (histogram and probability plots) and the Kolmogorov-Smirnov test. Difference in mean age between the genders was analyzed using the Mann-Whitney-U test, and the frequency of HDV-RNA positivity was compared between age groups and genders by the Pearson's chi-square test. A p value of less than 0.05 was considered statistically significant.

Results

Of the 2089 patients in this study, 1180 (56.5%) were male and 909 (43.5%) were female. The mean age of the patients was 46.3±15.3 years (1-97). The mean age of male and female patients was 46.3±15.3 and 46.4±15.2 years, respectively. There was no statistically significant difference in mean age between genders (p=0.79). The frequency of anti-HDV positivity in all patients was 4.1% (85/2089). Of the anti-HDV positive patients, 42 (49%) were male and 43 (51%) were female and there was no difference in anti-HDV positivity between genders (p=0.18). The mean age of the anti-HDV-positive patients was 49.5±11.1 years. When the distribution of anti-HDV-positive patients with respect to age groups was examined, a significant increase was found in the 50-59 years age group (p=0.02) (Figure 1).

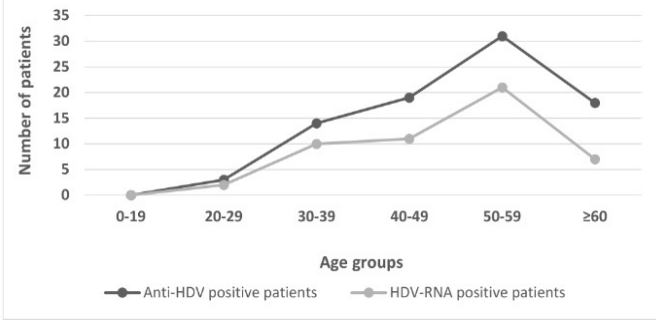

Figure 1. Distribution of anti-HDV and HDV-RNA positive patients according to age

HDV: Hepatitis delta virus

HDV-RNA was detected in 51 of 85 anti-HDV-positive patients. The frequency of HDV-RNA positivity was 2.4% (51/2089). The mean age of the HDV-RNA-positive patients was 48.7±11.5 years. Of the HDV-RNA-positive patients, 27 (53%) were male and 24 (47%) were female. There was no difference in HDV-RNA positivity between the genders (p=0.41). When the distribution of the HDV-RNA-positive patients was examined according to age groups, it was observed that the number of patients was highest in the 50-59 age group, but the difference was not statistically significant (p=0.23). The demographic and laboratory characteristics of the HDV-RNA-positive patients were shown in Table 1. Median HBV-DNA viral load (20 IU/mL) in HDV-RNA-positive patients was lower than in HDV-RNA-negative patients (62 IU/mL), but no statistically significant difference was found (p=0.09).

Table 1. The demographic and laboratory characteristics of patients with hepatitis delta virus-RNA positive

		HDV-RNA positive patients (n=51)
Age (years) (mean ± Standard deviation)		48.7±11.5
Gender n (%)	Female	24 (47%)
	Male	27 (53%)
HDV-RNA viral load (Copy/mL) (median)		39200 (IQR: 1250-356476)
HBV-DNA viral load (IU/mL) (median)		20 (IQR: 20-45)
HBV-DNA (n)	Positive	28
	Negative	23
Liver biopsy*	Fibrosis score (0-6) (median)	3
	Histological activity index (2-16) (median)	8

*The liver biopsy was evaluated by Modified Knodell scores
HDV: Hepatitis delta virus, IQR: Interquartile range, (range between the 25th to 75th percentiles), HBV: Hepatitis B virus

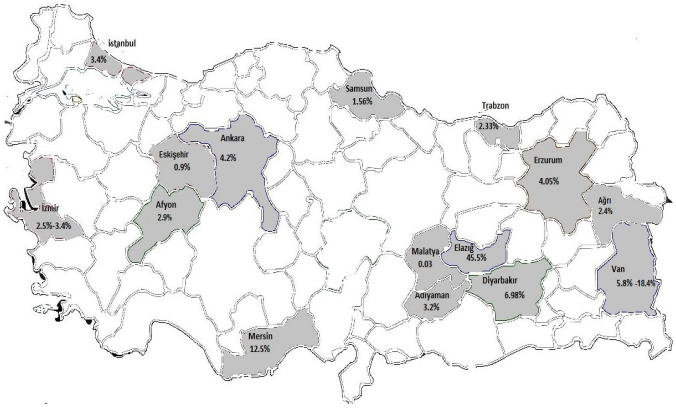

Figure 2. Anti-HDV seroprevalance in several areas of Turkey

Discussion

Despite the widespread application of HBV vaccine, HDV infection continues to be a global health problem, even in some developed countries, including some European countries, the US and Australia (1). The World Health Organization reported that there were globally 240 million people chronically infected with HBV, and about 15 million individuals chronically infected with both HDV and HBV. Globally, it is estimated that 5% of HBsAg-positive people are coinfected with HDV (11). Epidemiological studies indicate that the rate of anti-HDV positivity is lower in the Far Eastern countries with high HBV endemicity and higher in the Mediterranean countries with moderate HBV endemicity (12). As in the world, HDV frequency also shows regional differences in Turkey (Figure 2) (12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28). Higher rates were reported in the Eastern and Southeastern Anatolian regions. Regional studies on seroprevalence of anti-HDV in Turkey showed a rate of 2.5% to 3.4% in the Western Anatolia region, 0.9% to 15% in the Central Anatolia region, 0.3% to 45.5% in the Eastern Anatolia region and 3.2% to 6.98% in the Southeastern Anatolia region. The reported rate of anti-HDV seroprevalence in studies performed in Turkey varies between 0.3% and 45.5% showing regional differences (21,28). In a study conducted in Istanbul, the frequency of anti-HDV positivity in patients with chronic HBV infections was 3.4% (46/1339) (13). There are limited studies on the prevalence of HDV in Istanbul. In this study, anti-HDV seroprevalence was found to be 4.1% (85/2089) and HDV-RNA positivity was 2.4% (51/2089) in 2089 HBsAg positive patients. The cause of detection of lower rates of HDV-RNA compared to anti-HDV may be related to the fact that anti-HDV antibodies may remain after recovery.

There are a limited number of HDV-RNA studies reflecting the true HDV prevalence in Turkey. The frequency rate of HDV-RNA positivity in 547 HBsAg-positive patients was found to be 0.9% in a study conducted in the Central Anatolia, Turkey (17). In the Western region of Turkey, the rate of HDV-RNA positivity in 88 patients was found to be 2.3% (13). In a study conducted in 180 patients in Southeastern Anatolia, HDV-RNA positivity was detected in only two patients (27). In their study including 282 patients performed in Eastern Anatolia, Bahcecioglu et al. (28) reported that 23.4% of the subjects were HDV-RNA-positive. In this study, the frequency of HDV-RNA positivity was 2.4% (51/2089). Immunization with hepatitis B vaccine and the exclusion of high-risk blood donors before blood donation may be associated with low prevalence rates. High prevalence rates may be related to the fact that the studies were conducted in regions where HBV is high endemic and in patients with chronic HBV infection.

In a study performed in Romania, anti-HDV positivity was found in 223 (20.4%) of 1094 patients with chronic HB infection. Hepatitis D viremia was detected in 67.7% of these patients (29). In another study conducted in Romania, anti-HDV IgG seroprevalence was found 23.1% in 2761 HBsAg-positive patients, whereas HDV-RNA was positive in 16.4% of these patients (30). The rate of anti-HDV seroprevalence was reported as 7.7% in 169 chronic HBV cases in Saudi Arabia, whereas only four patients were HDV-RNA-positive (31). HDV-RNA is an important parameter for determining the true HDV prevalence, because anti-HDV may remain positive for many years after infection, or antibodies against HDV infection may not

be detected in the window period. In this study, the anti-HDV positivity rate was 4.1% and the HDV-RNA positivity rate was 2.4% in 2089 HBsAg-positive patients. In Turkey, although the rates have decreased in the Western Anatolia region, the prevalence of HDV infection is still at high levels in the Eastern Anatolia region. However, the decline in these rates may be related to sociocultural and socio-economic improvements, good laboratory practices in the screening of blood and blood products.

Long-term studies have shown a decrease in HDV seroprevalence in some endemic regions. Infection rates have decreased especially in young patients. HDV infections in Italy have been reported to be limited to those infected around the 1980s. As well as improvements in socio-economic and hygiene conditions, media campaigns for mass vaccination programs are thought to play a role in this decline in incidence rates in Italy (32). It has been reported that there was also a decrease in prevalence rates in Spain, India, Taiwan and Turkey (33,34,35).

In the present study, the mean age of the anti-HDV-positive patients was 49.5±11.1 years, and a significant increase in anti-HDV positivity was detected in the 50-59 age group. Similar results were found in studies conducted in our country (14,36). Unlike this study, in a study conducted in the UK, the median age of 82 anti-HDV-positive patients was 36 years. The low median age was thought to be related to migration from endemic regions and intravenous drug use (37). In another study examining the anti-HDV seroprevalence in 362 patients aged between 4 and 70 in Pakistan, 212 patients (58.6%) with a mean age of 29.75±11.27 years were found to be anti-HDV-positive. The higher rates of anti-HDV positivity in young adults were thought to be associated with injectable drug abuse and the use contaminated needles for therapeutic injections in this age group (38). Sexual transmission may be another possible route that leads to these higher prevalence rates (38). In this study, high anti-HDV positivity rates in older ages may be related to the vaccination program implemented in Turkey for more than 20 years and the family screening programs for patients with hepatitis B.

This study has some limitations; due to its retrospective design, the clinical data of the patients and data regarding the clinical course of HBV infection could not be obtained.

Conclusion

The anti-HDV rates detected in this study were consistent with regional data in Turkey, but lower than in studies conducted in the Eastern region of the country. In addition, HDV viremia was detected in only 60% (51/85) of anti-HDV-positive patients. It is important to investigate HDV-RNA to determine the true prevalence of HDV because anti-HDV antibodies may remain after recovery.

Acknowledgements: The authors thank for the technical assistance of Ümit Çetin.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (approval number: 2017/651/11).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Y., Design: A.Y., N.K., S.A., A.A., Data Collection or Processing: A.Y., N.K., S.A., M.Ö., M.B., M.G., A.A., Analysis or Interpretation: A.Y., N.K., Literature Search: A.Y., S.A., Writing: A.Y., N.K., S.A.

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

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

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Research Article

19

Doi: 10.4274/vhd.galenos.2018.0026
Viral Hepatitis Journal 2019;25(1):19-24

Sixteen-year Prognosis of Treatment-naive Patients with Hepatitis C Infection

Naiv Hepatit C Enfeksiyonlu Hastaların On-altı Yıllık Prognozu

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ABSTRACT

Objectives: In this study, we aimed to evaluate the clinical course of treatment-naive patients infected with hepatitis C virus (HCV) who were followed up in various centers in Turkey.

Materials and Methods: This was a retrospective study performed with the participation of 15 centers. Patients aged 18 years and older with HCV infection were included.

Results: A total of 391 treatment-naive patients infected with HCV were included in this study. During the follow-up period, the final values of alanine aminotransferase, aspartate transaminase, and total protein were significantly decreased when compared to the initial values (p<0.001, p<0.001, and p=0.005, respectively). In the study group, 19.2% of the patients underwent liver biopsy and 4.1% underwent transient elastography (FibroScan). An increased histological activity index (HAI) score and fibrosis in the second biopsy were observed in one patient, only increased HAI in two patients and increased fibrosis in one patient, as shown on the FibroScan. In the 16 years of the study period, cirrhosis was radiologically detected in only one patient.

Conclusion: Even if rapid progression is not observed, close monitoring of the clinical findings related to liver failure and fibrosis with invasive or non-invasive methods may be useful.

Keywords: Hepatitis C, naive, prognosis

ÖZ

Amaç: Bu çalışmada ülkemizin çeşitli merkezlerinde takip edilen naiv hepatit C virüs (HCV) ile enfekte hastaların klinik seyrini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu çalışma retrospektif olarak 15 merkezin katılımıyla gerçekleştirilmiştir. Çalışmaya 18 yaş üstü, HCV enfeksiyonu olan hastalar dahil edilmiştir.

Bulgular: Çalışmada 391 tedavi-naiv HCV enfeksiyonlu hasta yer almıştır. Hastaların takip süresinde son alanine aminotransferase, aspartate transaminase ve total protein değerleri ilk düzeyine göre önemli düzeyde azalmıştır (sırasıyla p<0,001, p<0,001, p=0,005). Çalışma grubunda hastaların %19,2'sine karaciğer biyopsisi, %4,1'ine elastografi (FibroScan) uygulanmıştır. Takip esnasında bir hastada ikinci biyopside histolojik aktivite indeksi (HAI) ve fibroziste artma, iki hastada sadece HAI'da artma, birinde FibroScan ile fibrozis değerinde artma olduğu gözlenmiştir. Bir hastada 16 yıl içinde radyolojik olarak siroz saptanmıştır.

Sonuç: Hızlı progresyon gözlenmemekle birlikte hastaların izleminde karaciğer yetmezliği ile ilgili klinik bulguların ve invaziv veya non-invaziv yöntemlerle fibrozisin yakın takibi yararlı olabilir.

Anahtar Kelimeler: Hepatit C, naiv, prognoz

Karacaer Z, Tosun S, Batirel A, Acar A, Çelik N, Uğuz M, Yavuz S, Yenilmez E, Doğan M, Yanık Yalçın T, Ergut Sezer B, Öztoprak N, Aydın Ö, Yıldız İE, Kostakoğlu U, Ergen P, Çetinkaya RA, Durmuş G, Gözüküçük R, Coşkuner SA, Artuk C, Göktaş EF, Güven E, Bekçibaşı M. Sixteen-year Prognosis of Treatment-naive Patients with Hepatitis C Infection. 2019;25:19-24.

Introduction

According to the data from the World Health Organization (WHO), there are 80 million people with chronic hepatitis C (CHC) infection worldwide. Each year, an estimated 700.000 people die from complications of hepatitis C (1). In the natural course of acute Hepatitis C virus (HCV) infection, most patients are asymptomatic. Due to the fact that only 10-15% of patients are symptomatic, few people are diagnosed during the acute phase (2). About 15-45% of infected persons spontaneously clear the virus within six months of infection without any treatment. The remaining will develop CHC infection. CHC is usually recognized during routine scans or after liver disease develops (3).

Although it varies depending on the patient's characteristics and behaviors, such as intensive alcohol use and substance abuse, the risk for developing cirrhosis within 20 years is 15-20% in CHC patients, while the risk for developing hepatocellular carcinoma (HCC) in one year is 2-4% in CHC patients with cirrhosis (3). Perz et al. (4) reported that HCV was the causative factor in 27% patients with cirrhosis and 25% of patients with HCC, globally. In a study from Turkey, Alacacioglu et al. (5) showed that HCV was involved in the etiology of HCC in 21.3% of 221 patients.

In this study, we aimed to evaluate the clinical course in HCV-infected patients who were followed in various centers in Turkey.

Materials and Methods

This was a retrospective study with the participation of 15 centers from Turkey. Patients over 18 years of age, who presented to the infectious diseases and clinical microbiology or gastroenterology outpatient clinics for HCV infections, were included the study.

The patient files were used to obtain the following: patient demographics, biochemical, microbiological, radiological, and histopathological outcomes, the diagnostic method, reasons for not undergoing treatment, and changes in the biochemical, microbiological, radiological, and histopathological findings found during the follow-up.

The principles of the Declaration of Helsinki and Good Clinical Practice Guideline were respected during the entire process of enrolling the patients in the study and collecting/analyzing/reporting the data. This study was approved by the Local Ethics Committee İzmir Bozyaka Training and Research Hospital, (approval number: 22/11/2016-1). Informed consent was obtained from all participants.

Statistical Analysis

The study data was transferred to SPSS IBM 22.0 (SPSS Inc., Chicago, IL, United States of America) statistical software and analyzed. The distribution of the data was evaluated using the Kolmogorov-Smirnov test. The descriptive findings of the data as determined by counting were expressed as frequency distribution and percentage, while the measured and non-normally distributed data were expressed as median (minimum-maximum). The initial and final laboratory data of each patient during the follow-up were compared using the Wilcoxon signed-rank test. A p value of less than 0.05 was considered statistically significant.

Results

A total of 391 treatment-naive patients with HCV infection were enrolled in this study. The median age of the patients was 53 (19-85) years, with 58.3% males and 41.7% females. The median duration of follow-up was 651.5 (8-5827) days; 51.9% were followed for ≤5 years, 8.4% for 6-10 years, 2% for 11-15 years, and 37.6% for ≥16 years.

Distribution of patients with HCV infection according to time of diagnosis was 0.5% in 1992-1995, 5.4% in 1996-2000, 7.4% in 2001-2005, 14.8% in 2006-2010, and 71.9% in 2010-2016. In general, the number of patients who maintained regular control examination was low and significantly increased in 2016 (Table 1).

Laboratory findings at the time of diagnosis as median values were as follows: alanine aminotransferase (ALT): 43 (7-872) U/L, aspartate aminotransferase (AST): 36.5 (7-1.287) U/L, γ-glutamyltransferase (GGT): 29 (7-2.558) U/L, total bilirubin: 0.7 (0-11) g/dL, HCV RNA: 285.003 (0-95.000.000) IU/mL, platelets 238.000 (56.000-787.000) cells/μl, α-fetoprotein (AFP): 3.13 (0-300) ng/mL, total protein: 7.2 (4-9) g/dL, and albumin: 4.1 (3-6) g/dL.

Laboratory findings at the end of follow-up were as follows: ALT: 30 (5-259) U/L, AST 30 (5-199) U/L, GGT: 28 (4-602) U/L, total bilirubin: 0.6 (0.1-10) g/dL, HCV RNA: 50.180 (0-56.000.000) IU/mL, platelets: 232.500 (70.000-4.500.000) cells/μl, AFP: 3 (0-24) ng/mL, total protein: 7.1 (4-9) g/dL, and albumin: 4 (0-7) g/dL.

During the follow-up, the final ALT, AST, and total protein values were significantly decreased when compared with the initial values ($p<0.001$, $p<0.001$, and $p=0.005$, respectively). No significant differences were found in the HCV RNA, platelets, GGT, total bilirubin, AFP, and albumin levels ($p=0.542$, $p=0.976$, $p=0.464$, $p=0.248$, $p=0.933$, and $p=0.220$, respectively). According to the follow-up period, ALT decreased significantly in each period, except ≥16 years, while AST was decreased in 0-5 years and 11-15 years, total protein decreased only in the first five years (Table 2).

Seventy-five of the patients in the study group underwent liver biopsy; the median histological activity index (HAI) value was 6 (1-6) and the median fibrosis value was 1 (0-6). In the same time period, only 16 patients underwent FibroScan testing, with a median fibrosis value of 1 (0-4) in these patients.

Table 1. Distribution of control examinations according to years

Year	Frequency	Percent
2001	3	0.8
2002	1	0.3
2003	3	0.8
2004	2	0.5
2006	5	1.3
2007	1	0.3
2009	1	0.3
2010	4	1
2011	2	0.5
2012	7	1.8
2013	9	2.3
2014	10	2.6
2015	37	9.5
2016	162	41.4

Table 2. Distribution of first and last laboratory findings according to the follow-up period median (minimum-maximum)

		ALT	AST	GGT	T.BIL	HCV RNA x10³	PLT x10³	AFP	T.PRT	ALB
≥5 years (n=203)	First	40 (8-721)*	34 (8-1287)*	28 (7-2558)	0.6 (0-11)	222 (0-16000)	235.5 (56-787)	3.1 (0-28)	7.2 (4-9)*	4.1 (3-6)
	Last	32 (5-220)	32 (5-199)	28 (5-602)	0.6 (0,1-10)	48.4 (0-18230)	231 (70-515)	3 (0-24)	7.1 (4-9)	4 (0-7)
6-10 years (n=33)	First	30 (10-213)*	29 (7-117)	26 (7-235)	0.7 (0-7)	266.5 (0-95000)	266 (87-404)	3.1 (0-36)	7.3 (6-9)	4.1 (3-5)
	Last	25 (9-155)	25 (12-76)	21.5 (4-118)	0.6 (0.2-1.9)	84 (0-14000)	252 (120-450)	3.25 (0-21)	7.2 (6-9)	4.2 (3-6)
11-15 years (n=8)	First	60 (24-383)*	45 (30-201)*	25 (10-289)	1	1 (0.009-391)	231 (204-381)	3.45 (3-4)	6.95 (7-8)	4
	Last	26 (18-259)	34 (18-139)	35 (10-263)	0.6 (0.3-1.5)	1.3 (0-56000)	269 (206-316)	4.1 (3-15)	7.5 (6-8)	4.37 (4-5)
16≤ years (n=147)	First	47 (7-872)	42 (11-1076)	31 (10-522)	0.7 (0-5)	602 (0-47023)	239 (57-787)	3.2 (0-300)	7.2 (6-9)	4 (3-6)
	Last	20 (20-108)	29 (23-49)	31 (13-38)	1.35 (0.9-1.8)	0.179 (0-0.359)	231 (138-415)	3.81 (3-5)	8	4.35 (4-5)

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: γ-glutamyltransferase, T.BIL: Total bilirubin, HCV: Hepatitis C virus, PLT: Platelet, AFP: α-fetoprotein, T.PRT: Total protein, ALB: Albümin, *p<0.05

Table 3. Results of control biopsy and FibroScan

Patients No	1. Biopsy		2. Biopsy		3. Biopsy		1. FibroScan	2. FibroScan
	HAI	Fibrosis	HAI	Fibrosis	HAI	Fibrosis	-	-
1	5	1	6	2	6	2	4	4
2	7	1	7	1	-	-	3	3
3	3	0	İnadequate material		-	-	1	1
4	3	1	5	1	4	0	1	2
5	3	1	5	1	-	-	0	0
6	8	3	8	3	-	-	2	2
7	8	2	8	2	-	-	1	1

HAI: Histological activity index

Only seven patients underwent a second and two patients a third biopsy during the follow-up period. The HAI and fibrosis were increased in one patient in whom treatment could not be initiated due to discontinued follow-up, while only the HAI was increased in two patients who did not require or rejected treatment (Table 3). Seven of the patients underwent a second FibroScan during the follow-up period. The fibrosis value evaluated using FibroScan was increased in one patient, but no changes occurred in the remaining six patients. The reasons for not undergoing treatment could not be determined in patients with increased fibrosis scores (Table 3).

At first, two patients were diagnosed with cirrhosis through ultrasonography. In one patient in whom the initial HAI was 14/18 and fibrosis was 4/6, cirrhosis was radiologically stable over the 16 years. The reasons for not undergoing treatment could not be established in patients who developed cirrhosis.

Genotypic analysis was performed in 24.4% of the patients; 51.1% were genotype 1b, 34% were genotype 1, 12.8% were genotype 1a, and 1.1% were genotype 1c and genotype 3a.

Overall, the reason for not receiving treatment could only be determined in 56.3% of patients. The order of frequency of reason that were determined was as follows: interferon (IFN) contraindication or intolerance in 47.3%, refusing treatment in 21.8%, waiting for new treatment options in 14.5%, lost to follow-up in 7.3%, requiring no treatment yet in 3.2%, treatment was planned but not yet initiated in 2.7%, patient healing without treatment in 0.5%, and lost of the patient for any other reason in 0.5%.

Discussion

In our study, it was observed that the CHC diagnosis frequency has increased over the last six years. A significant increase was also observed in the number of patients who attended routine control within the last one year. This may be related to the HCV scanning tests included in the mandatory tests for blood donation, operations, or marriage procedures, etc. as well as an increase in the societal awareness of this infection. In addition, the recent introduction of direct-acting antiviral treatments in some countries may be a factor in the increase in the presentation of those patients who desire access to these treatment modalities.

CHCV infection often follows a progressive course over many years and can ultimately result in cirrhosis, HCC, and need for liver transplantation. Therefore, it is recommended to keep this condition under control; for example, harmful habits in CHC patients (such as alcohol abuse) should be reduced, hepatitis B vaccination measures should be taken, and the liver fibrosis level should be evaluated. In addition, a proper treatment regimen should be determined while considering several parameters, such as the genotype, comorbidity, pregnancy, and drug-drug interactions, and the efficacy and toxicity of the treatment should be monitored (3). Moreover, human immunodeficiency virus and/or HBV have been found to be associated with a poor prognosis in HCV infection. Obesity and metabolic syndromes increase the incidence of non-alcoholic fatty liver disease, which in turn causes increased fibrosis in CHC patients. Therefore, increases in insulin resistance and weight should be prevented in the follow-up of these patients with proper diet, exercise, and medical treatments (6).

In this research, it was found that no significant changes occurred in the biochemical and microbiological data during the follow-up, with the exception of the levels of ALT, AST, and total protein in the first five years. However, it has been observed that the change in ALT levels lasted longer. Biochemical and serological tests are good prognostic factors for determining low fibrosis or the absence of fibrosis in the follow-up of HCV patients. However, these tests are insufficient for the diagnosis of advanced fibrosis or cirrhosis (7). An overall evaluation of the severity of liver disease is recommended before treatment, and the identification of cirrhosis or advanced fibrosis is important for both the determination of the treatment options and prognosis after treatment (8). Therefore, the development of fibrosis should be monitored with non-invasive biochemical methods during the patient follow-up, however, when fibrosis is suspected, it may be necessary to go through the more diagnostic methods.

Progression was observed in only one of the seven patients in this study in whom the histopathological controls could be done. The frequency of follow-up with liver biopsy or ultrasonography was low, however, HCV infection did not show rapid courses in the study group, and clinical cirrhosis findings were not observed. Poynard et al. (9) reported a yearly progression rate of 0.133 fibrosis unit in CHC patients. They found that progression of fibrosis was influenced by male gender, age of initial infection >40, and alcohol consumption >50 g/day, but the genotype had no effect. The authors also found that cirrhosis developed within an average of 30 years in untreated patients. Moreover, while cirrhosis developed

within 20 years in 33% of patients, it did not develop in 31% of patients, or no progression was seen within at least 50 years.

In one prospective study, it was found that survival in CHC patients decreased with the presence of cirrhosis, prolonged disease duration, a history of intravenous drug use, and intensive alcohol consumption, but increased with antiviral treatment. Even if there was no cirrhosis at the time of diagnosis, acquiring the disease at an early age significantly increased mortality (8). Although the viral load is an important parameter related to treatment, its effects on the prognosis could not be demonstrated (10). It could be reasonable to evaluate liver fibrosis after the diagnosis in patients with HCV infection detected at an advanced age, as well as those having harmful habits. A liver biopsy is the gold standard, and because it is an expensive and invasive procedure, the WHO recommends the use of non-invasive methods such as aspartate transaminase-to-platelet ratio index (APRI), fibrosis-4 index (FIB-4), or FibroScan in low- and middle-income countries (3). A non-invasive method can also be preferred in cases in which a biopsy cannot be performed.

Based on the results of our study, histopathological and FibroScan examinations were not used frequently. Until recently, liver biopsy was not required in CHC patients in order to start treatment in Turkey. This may be the reason why radiological and histopathologic evaluations are not performed frequently. Moreover, FibroScan is not available in every center in our country.

Should every patient be treated? Studies using regimens with IFN report that, although the risk of HCC continues in patients with advanced fibrosis who developed a virological response, the liver related morbidity and mortality and the incidence of liver transplantation/death are significantly related (11,12,13). In addition, symptoms and mortality due to severe extrahepatic involvement can also be reduced with HCV treatment. Recent data has shown that antiviral therapies also increase the quality of life in CHC patients (6). Moreover, the WHO declared "2030 target" to eliminate HCV, but in order to achieve this target, protection measures must be expanded, and at least 80% of patients must be treated (1).

The current guidelines recommend initiating antiviral therapy in all patients infected with HCV, except for those with short life expectancy for reasons other than liver disease. When this is not possible, there has been a common consensus that it would be appropriate to treat the high-risk population for the complications of the disease or contagion. It is recommended to avoid delays in treatment for patients with advanced fibrosis and cirrhosis (6,8).

Although all HCV-infected patients are treated in high-income countries, if there are no contraindications, the treatment is decided according to the level of fibrosis in low- and middle-income countries (3). In Turkey, until recently, the detection of HCV-RNA positivity was sufficient to start treatment. However, several criteria (such as genotypic analysis and histopathological examination) were implemented in 2016 after the development of direct-acting antiviral therapies.

In the present study, about half of the patients remained untreated because they could not use IFN-containing regimens. A similar situation was demonstrated in a study by Güner et al. (14). However, our patients with observed progression were not included in this group. Since histopathological examination was rarely performed, it was not possible to establish a cause-effect relationship between the introduction of alternative IFN treatments and the progression with the results of this study.

Since a significant number of patients were followed up for 10 years or longer, including the data demonstrating the prognosis of those CHC patients who were not undergoing treatment makes the present study different from previous similar studies. However, our study has several limitations. First, the lack of generalized rules about the follow-up of the disease caused the centers to exhibit different approaches. Therefore, there was a lack of radiological, biochemical, and/or histopathological data in some of the patients, causing difficulty in comparing the results. In addition, since the histopathological and radiological follow-up rates were low, the cirrhotic patients might not have been sufficiently evaluated. Another limitation was that the presence of HCV-related complications and their effects on the prognosis were not evaluated. Therefore, further prospective studies are warranted.

Conclusion

HCV infection is a disease in which the diagnosis may be delayed because of its silent progression. Even if rapid progression is not observed, close monitoring of the clinical findings related to liver failure and fibrosis with invasive or non-invasive methods may be useful.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee (İzmir Bozyaka Training and Research Hospital, approval number: 22/11/2016-1).

Informed Consent: Informed consent was received from all.

Peer-review: Externally peer-reviewed.

Author contributions

Concept: S.T., Design: S.T., Supervision: S.T., A.A., A.B., N.Ç., M.U., S.Y., E.Y., M.D., T.Y.Y., B.E.S., N.Ö., Ö.A., İ.E.Y., U.K., P.E., R.A.Ç., G.D., R.G., S.A.C., C.A., E.F.G., E.G., M.B., Data Collection or Processing: A.B., N.Ç., M.U., S.Y., E.Y., M.D., T.Y.Y., B.E.S., N.Ö., Ö.A., İ.E.Y., U.K., P.E., R.A.Ç., G.D., R.G., S.A.C., C.A., E.F.G., E.G., M.B., Analysis or Interpretation: Z.K., Literature Search: Z.K., S.T., Writing: Z.K., S.T., A.A., A.B., Critical Reviews: Z.K., S.T., A.A., A.B., N.Ç., M.U., S.Y., E.Y., M.D., T.Y.Y., B.E.S., N.Ö., Ö.A., İ.E.Y., U.K., P.E., R.A.Ç., G.D., R.G., S.A.C., C.A., E.F.G., E.G., M.B.

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

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

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Research Article

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Doi: 10.4274/vhd.galenos.2019.0006
Viral Hepatitis Journal 2019;25(1):25-31

Impact of Direct Acting Antiviral Agents on Psychiatric and Sexual Health of Patients with Hepatitis C Virus

Direkt Etkili Antiviral İlaçların Hepatit C Hastalarının Psikiyatrik ve Cinsel Sağlıkları Üzerine Etkileri

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ABSTRACT

Objectives: Data about the psychosocial side effects of direct-acting antiviral agents (DAA) used for the treatment of hepatitis C virus (HCV) infection is scarce. In this study, it is aimed to assess the psychiatric and sexual effects of ledipasvir/sofosbuvir (L/S) combination and paritaprevir-ritonavir-ombitasvir-dasabuvir (PROD) combination in patients with HCV infection.

Materials and Methods: The sample of this retrospective study consisted of patients who were diagnosed with HCV infection and received PROD or L/S treatment. The patients were assessed by the Hospital Anxiety and Depression (HAD) scale and Arizona Sexual Experiences (ASEX) scale at baseline and first-, third- and sixth-month visits. Besides these, demographic data and data about the liver disease were collected.

Results: During the studied period, 42 patients were started DAA treatment. The average age of the sample was 56.64±12.04 years. Thirty-five (83.3%) patients achieved sustained viral response. Data of the patients who filled HAD or ASEX at baseline and at least in one of the following visits within six months were used. Anxiety, depression and sexual measures did not differ between baseline and following assessments.

Conclusion: L/S and PROD do not seem to have a significant effect on anxiety and depression levels and sexual experiences of the patients while they made an improvement in viral load.

Keywords: Anxiety, sexual dysfunction, depression, direct acting antiviral agents, hepatitis C virus, adverse effects

ÖZ

Amaç: Hepatit C tedavisinde kullanılan direkt etkili antiviral ajanların (DAA) psikososyal yan etkileri ile ilgili veri çok sınırlıdır. Bu çalışmada ledipasvir/sofosbuvir (L/S) kombinasyonu ile paritaprevir-ritonavir-ombitasvir-dasabuvir (PROD) kombinasyonunun hepatit C virüsü (HCV) ile enfekte hastalardaki psikiyatrik ve cinsel etkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmanın örneklemini HCV enfeksiyonu tanısı konan ve PROD ya da L/S tedavisi görmüş olan hastalar oluşturmaktadır. Hastalar tedavi öncesi ilk vizit ile birinci, üçüncü ve altıncı aylardaki vizitlerde Hastane Anksiyete Depresyon (HAD) ölçeği ve Arizona Cinsel Yaşantılar (ACYÖ) ölçeği ile değerlendirilmişlerdir. Bunların yanı sıra hastaların demografik ve karaciğer hastalığı ile ilgili verileri de çalışmada kullanılmıştır.

Bulgular: Çalışma dönemi sürecinde 42 hastaya DAA başlanmıştır. Örneklemin ortalama yaşı 56,64±12,04'tür. Hastaların 35'inde (%83,3) kalıcı viral yanıt sağlanabilmiştir. Bazı hastaların ölçekleri tam olarak doldurmaması nedeniyle bazal ve takip eden altı ay içindeki en az bir vizitte HAD ya da ACYÖ'yü dolduran hastaların verileri kullanılmıştır. Anksiyete, depresyon ve cinsel yaşantı ile ilgili ölçümler açısından bazal ve izlemdeki değerlendirmeler arasında bir farklılık saptanmamıştır.

Sonuç: L/S ve PROD tedavileri viral yük açısından iyileşme sağlarken, anksiyete ve depresyon düzeyleri ile cinsel yaşantı üzerinde belirgin bir etki göstermemiştir.

Anahtar Kelimeler: Anksiyete, cinsel disfonksiyon, depresyon, direkt etkili antiviral ilaçlar, hepatit C virüsü, istenmeyen etkiler

Kuman Tunçel Ö, Akyol D, Pullukçu H, Yamazhan T, Işıkgöz Taşbakan M, Önen Sertöz Ö. Impact of Direct Acting Antiviral Agents on Mental and Sexual Health of Patients with Hepatitis C Virus. 2019;25:25-31.

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Introduction

Hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease and there are approximately 71 million chronically infected individuals globally (1,2). The prevalence of HCV infection varies from country to country. For Turkey, findings of Tozun et al. (3) revealed anti-HCV positivity in 1% of the adult population. Genotype 1b is the most common HCV genotype in Turkey (4,5,6,7).

Hepatitis C treatment showed significant changes over the years. Sustained viral response (SVR) rates of up to 99% have been reported with combinations of direct-acting antivirals (DAAs) (8,9). The use of sofosbuvir/ledipasvir (S/L) and paritaprevir-ritonavir-ombitasvir-dasabuvir (PROD) combinations was approved by the FDA in 2014 (10) and reimbursement started in 2016 in our country (11).

Interferon treatment has many psychiatric side effects such as irritability, anger, anxiety, emotional instability, fatigue, sleep disturbances and severe depression (12,13,14). DAAs are assumed to provide higher cure rates with fewer side effects. The most common reported side effects for L/S are fatigue, headache and nausea (9), and for PROD are insomnia, rash, redness of the skin, itchy skin, swollen throat, face, tongue, lips, hands, feet, ankles, or lower legs, weakness, and confusion (15). In ION and PEARL studies which establish safety and efficacy for L/S and PROD respectively, no psychiatric serious adverse events were reported (9,16,17). Insomnia and irritability were among the common adverse events for both. In a recent study, anxiety (7.1%), depression (12.6%) and insomnia/sleep disorders (14%) were reported among the DAA-related adverse events (18). The rate of psychiatric disorders in the DAA group was identical to those observed in the placebo group in that study. In most of the clinical trials of DAAs, anxiety, depression or sexual side effects were not specifically focused. Sundberg et al. (19) published the first study that monitored psychiatric adverse effects of daclatasvir, sofosbuvir and simeprevir in a sample of 17 patients. They found that DAA treatment did not increase depressive symptoms or sleep disturbance with a high SVR of 88%. Gallach et al. (20) evaluated anxiety and depression status of 145 DAA-treated patients by Hospital Anxiety and Depression scale (HADS) (21) in their prospective study. They reported that anxiety and depression scores did not change during the follow-up period (treatment period and 12 weeks after). In a study sample of veterans with and without mental health diagnosis, there was no change in depression scores evaluated by the Patient Health Questionnaire, from baseline to end of the treatment (22). No psychiatric decompensation was reported while using DAA in that study.

For sexual side effects, Lenz et al. (23) reported a case of acute onset sexual dysfunction within the first month of the S/L treatment. Besides, it is known that HCV infection is strongly associated with sexual health issues. Karaivazoglou et al. (24) defined three patterns of sexual dysfunction in HCV-infected patients: pre-cirrhotic sexual impairment, cirrhosis-induced sexual decline and interferon-associated sexual difficulties.

Considering the paucity of studies in the field of psychiatric effects of DAA, we planned our study. We aimed to evaluate the psychiatric and sexual effects of S/L and PROD combinations that have recently been used in patients with chronic HCV infection.

Materials and Methods

This retrospective study was performed by the collaboration of the Ege University Hospital, Clinic of Infectious Diseases and Clinical Microbiology and Clinic of Psychiatry. The sample consisted of patients who were diagnosed with HCV infection and received PROD or L/S treatment. The physicians had decided to initiate DAA treatment in accordance with the guidelines. The duration of treatment was 12 weeks for PROD and, 12 or 24 weeks for L/S treatment depending on viral genotype and fibrosis stage. For this study, a negative test for HCV RNA at 12 weeks post-treatment was defined as SVR.

During their DAA treatment, anxiety and depression level of the patients was assessed by HADS (21). Besides, sexual side effects were evaluated by the Arizona Sexual Experiences scale (ASEX) (25). The patients filled the questionnaires at the baseline and first-, third- and sixth-month visits. In the adaptation and reliability studies of these scales for the Turkish population, 7 was found to be the cut-off score for depression subscale and 10 was found to be the cut-off score for anxiety subscale of the HADS (26); and 10 for the ASEX (27). Scores higher than these cut-off points were defined as depression risk, anxiety disorder risk and sexual dysfunction.

In this retrospective study, PROD or L/S treated patients' demographic data, anxiety and depression scores, sexual experience scores and data about HCV infection were collected. Patients gave consent to the use of their data. We have obtained approval for the study from the Infectious Diseases and Clinical Microbiology Department of Ege University.

Statistical Analysis

Data analyses were performed by IBM SPSS, version 21.0, for Windows. The Shapiro-Wilk test was used to analyze normality. Quantitative data were presented as mean and standard deviations if there is a normal distribution, as median and interquartile ranges if there is skewed distribution. To compare the paired data; for analysis of quantitative data, the paired sample t-test was used for the data with normal distribution, the Wilcoxon signed-rank test was used for the data with skewed distribution and for comparison of qualitative data, McNemar's test was used. An alpha level of 0.05 was set up to indicate statistical significance.

Results

During the study period, 42 patients were started DAA treatment (Figure 1). The average age of the sample was 56.64±12.04 years. Twenty-five (53.2%) of them were female. In the study sample, genotype 1b was present in 36 (85.7%) patients, genotype 1a in three, genotype 4 in two (4.8%) patients and, one patient had genotype 1 (2.4%), however, subclassification was not performed. Nine (21.4%) patients had cirrhosis. Twenty (47.6%) patients were previously treated with another treatment regimen, and 19 (45.2%) were treated with an interferon-based treatment. Viral load declined to 0 in all patients during the treatment period. Thirty-five (83.3%) patients achieved SVR, one (2.4%) patient was reinfected by another genotype and data of six (14.3%) patients about SVR are missing.

There was no significant correlation between baseline viral load and baseline depression, anxiety and ASEX scores. Most of the patients had not filled in the questionnaires completely. The flowchart of the patients is provided in Figure 1. Among 42

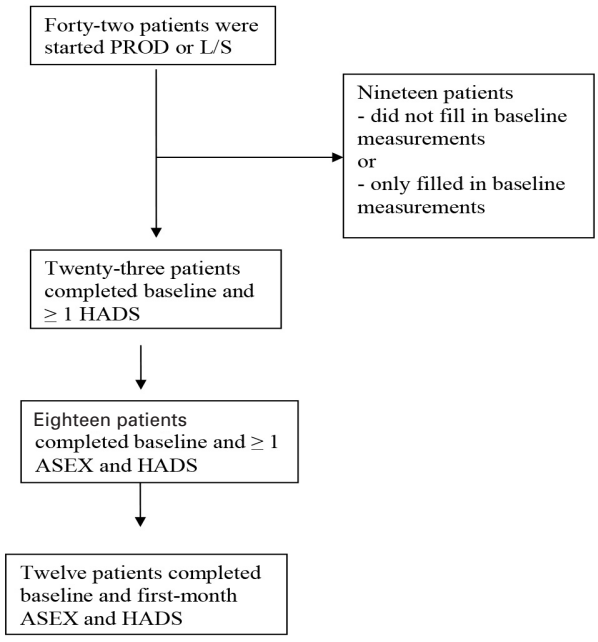

Figure 1. Flowchart of the study

ASEX: Arizona Sexual Experiences scale, HADS: Hospital Anxiety and Depression scale, L/S: Ledipasvir-sofosbuvir combination, PROD: Paritaprevir-ritonavir-ombitasvir-dasabuvir combination

patients, who were started PROD or L/S, 23 patients completed HADS questionnaire at baseline and at least in one of the following visits within six months. Among these 23 patients, four (36.4%) patients using PROD and seven (55.6%) patients using L/S were female. The average age of PROD group was 53.55±10.11 and of L/S group was 59.17±11.91 years. Comparison of their baseline scores with the following highest scores for HADS is given in Table 1. There was no significant difference in anxiety and depression scores between females and males at any time. No correlation was detected between age and depression or anxiety scores during follow-up. As the number of the patients, who were at risk for depression or anxiety disorder, was very low for each treatment group, the comparison between baseline and following visit results of these variables are made for the whole group (Table 1).

Eight patients using PROD and nine patients using L/S filled the HADS both at the beginning of the treatment and at the first month. Among these 17 patients; three (37.5%) patients using PROD and five (55.6%) patients using L/S were female. The average age of PROD group was 54.63±10.11 and of L/S group was 61.67±9.45 years. There was no significant difference between baseline and the first-month visit HADS scores while there was a significant decrement in the viral load (Table 2). As the number of patients, who were at risk for depression or anxiety disorder, was very low for each treatment group, the comparison between baseline and first-month results for these variables were made for the whole group.

Table 1. Comparison of the baseline measurements with the follow-up measurements on the basis of the Hospital Anxiety and Depression scale

Variable	Baseline		Follow-up		
	n	%	n		%
At risk for depression in PROD	0	0	1		8.3
At risk for depression in L/S	1	8.3	5		41.7
At risk for anxiety disorder in PROD	5	45.5	4		36.4
At risk for anxiety disorder in L/S	7	58.3	5		41.7
	n	**%**	**n**	**%**	**Statistics**
At risk for anxiety disorder (n=23)	12	52.2	9	39.1	p=0.375
At risk for depression (n=23)	1	4.3	6	26.1	p=0.063
	Mean	**SD**	**Mean**	**SD**	
HADS-A for PROD	5.64	4.23	5.73	3.82	T=-0.102, p=0.921
HADS-A for L/S	7	4.31	6.58	4.17	T=0.422, p=0.681
HADS-D for PROD	5	3	5.27	3.66	T=-0.346, p=0.736
HADS-D for L/S	5.42	4.62	7.58	5.66	T=-2.106, p=0.059
Viral load for PROD* (IU/mL)	368656.27	714263.58	0	0	Z=-2.366, p=0.018
Viral load for L/S (IU/mL)	1684255.33	1504357.84	0	0	T=3.878, p=0.003

The lowest viral load achieved, and the highest HADS-A and HADS-D scores within six months were used for follow-up measurements. PROD group consists of 11, L/S group consists of 12 patients.
*Viral load for PROD had a skewed distribution. The median values and interquartile ranges were 83888 and 372447 for baseline measurement and, 0 and 0 for the measurement made at the sixth month, respectively.
PROD: Paritaprevir-ritonavir-ombitasvir-dasabuvir combination, L/S: Ledipasvir-sofosbuvir combination, n: Number, SD: Standard deviation, HADS-A: Hospital Anxiety and Depression scale-anxiety subscale, HADS-D: Hospital Anxiety and Depression scale-depression subscale

Table 2. Comparison of the baseline measurements with first-month measurements on the basis of the Hospital Anxiety and Depression scale

Variable	Baseline		Month 1		
	n	%	n		%
At risk for depression in PROD	0	0	1		12.5
At risk for depression in L/S	1	11.1	3		33.3
At risk for anxiety disorder in PROD	5	62.5	4		50
At risk for anxiety disorder in L/S	6	66.7	3		33.3
	n	**%**	**n**	**%**	**Statistics**
At risk for depression (n=17)	1	5.9	4	23.5	p=0.250
At risk for anxiety disorder (n=17)	11	64.7	7	41.2	p=0.219
	Mean	**SD**	**Mean**	**SD**	
HADS-A for PROD	6.88	3.8	7	3.66	T=-0.111, p=0.915
HADS-A for L/S	7.78	4.29	6.33	3.67	T=0.189, p=0.268
HADS-D for PROD	5.62	3.07	5.25	3.62	T=0.287, p=0.783
HADS-D for L/S	6	5.12	7.56	5.25	T=-1.332, p=0.220
Viral load for PROD* (IU/mL)	199007	250336.4	8	15.5	Z=-2.512, p=0.012
Viral load for L/S (IU/mL)	1752842.11	1611888.21	41	45.98	T=3.262, p=0.011

PROD group consists of 8, L/S group consists of 9 patients.
*Viral load for PROD had a skewed distribution. The median values and interquartile ranges were 86013.5 and 364851 for baseline measurement and, 0 and 17 for the measurement made at the first month, respectively.
n: Number, L/S: Ledipasvir-sofosbuvir combination, SD: Standard deviation, PROD: Paritaprevir-ritonavir-ombitasvir-dasabuvir combination, HADS-A: Hospital Anxiety and Depression scale-anxiety subscale, HADS-D: Hospital Anxiety and Depression scale-depression subscale

Table 3. Comparison of the baseline measurements with the follow-up measurements on the basis of the Arizona Sexual Experiences scale

Variables	Baseline		Follow-up		
	n	%	n		%
Sexual dysfunction in PROD	8	80	9		90
Sexual dysfunction in L/S	5	62.5	8		100
At risk for depression in PROD	0	0	1		10
At risk for depression in L/S	0	0	2		25
At risk for anxiety disorder in PROD	5	50	4		40
At risk for anxiety disorder in L/S	4	50	2		25
	n	**%**	**n**	**%**	**Statistics**
Sexual dysfunction (n=18)	13	72.2	17	94.4	p=0.125
At risk for depression (n=18)	0	0	3	16.7	-
At risk for anxiety disorder (n=18)	9	50	6	33.3	p=0.375
	Mean	**SD**	**Mean**	**SD**	
ASEX for PROD	14.4	4.67	15.8	4.16	T= -1.520, p=0.163
ASEX for L/S	13.38	3.58	16.38	3.81	T= -3.310, p=0.013
HADS-A for PROD	6.2	3.99	6.1	3.81	T=0.104, p=0.919
HADS-A for L/S	6	3.16	5.88	3.8	T=0.092, p=0.929
HADS-D for PROD	5.2	3.08	5.3	3.86	T= -0.118, p=0.909
Viral load for L/S (IU/mL)	1645946.38	1719086.88	0	0	T=2.708, p=0.030
	Median	**IQR**	**Median**	**IQR**	
HADS-D for L/S	4	5.75	5	8.5	Z= -1.364, p=0.172
Viral load for PROD (IU/mL)	86013.5	453062	0	0	Z= -2.803, p=0.005

The lowest viral load achieved and the highest HAD-A, HAD-D and ASEX scores within six months were used for follow-up measurements. PROD group consists of 10, L/S group consists of 8 patients.
n: Number, PROD: Paritaprevir-ritonavir-ombitasvir-dasabuvir combination, L/S: Ledipasvir-sofosbuvir combination, SD: Standard deviation, ASEX: Arizona Sexual Experiences scale, HADS-A: Hospital Anxiety and Depression scale-anxiety subscale, HADS-D: Hospital Anxiety and Depression scale-depression subscale, IQR: Interquartile range

Table 4. Comparison of the baseline measurements with the first-month measurements on the basis of the Arizona Sexual Experiences scale

Variables	Baseline		Month 1		
	Mean	**SD**	**Mean**		**SD**
ASEX for PROD	14.88	4.58	15.63		3.58
ASEX for L/S	14	4.16	15.25		3.69
HADS-A for PROD	6.88	3.8	7		3.66
HADS-A for L/S	6.5	2.89	3.25		1.71
HADS-D for PROD	5.62	3.07	5.25		3.62
HADS-D for L/S	5	3.92	4.5		3.32
Viral load (IU/mL) for L/S	2343305.75	2145899.11	35.5		63.25
	Median	**IQR**	**Median**		**IQR**
Viral load (IU/mL) for PROD	86013.5	364	0		17
	n	**%**	**n**		**%**
Sexual dysfunction in PROD	7	87.5	8		100
Sexual dysfunction in L/S	3	75	4		100
At risk for depression in PROD	0	0	1		12.5
At risk for depression in L/S	0	0	0		0
At risk for anxiety disorder in PROD	5	62.5	4		50
At risk for anxiety disorder in L/S	2	50	0		0
	n	**%**	**n**	**%**	**Statistics**
Sexual dysfunction (n=12)	10	83.3	12	100	-
At risk for depression (n=12)	0	0	1	8.3	-
At risk for anxiety disorder (n=12)	7	58.3	4	33.3	p=0.375
	Mean	**SD**	**Mean**	**SD**	
ASEX (n=12)	14.58	4.27	15.5	3.45	t=-1.201, p=0.255
HADS-A (n=12)	6.75	3.39	5.75	3.57	T=1.049, p=0.317
	Median	**IQR**	**Median**	**IQR**	
HADS-D (n=12)	6	4.5	3.5	6.5	Z=-0.360, p=0.719
Viral load (IU/mL) (n=12)	356303	823297	0	20	Z=-3.059, p=0.002

PROD group consists of 8, L/S group consists of 4 patients.
SD: Standard deviation, ASEX: Arizona Sexual Experiences scale, PROD: Paritaprevir-ritonavir-ombitasvir-dasabuvir combination, L/S: Ledipasvir-sofosbuvir combination, HADS-A: Hospital Anxiety and Depression scale-anxiety subscale, HADS-D: Hospital Anxiety and Depression scale-depression subscale, IQR: Interquartile range, n: Number

Among 42, 18 patients completed the ASEX questionnaire at the baseline and at least in one of the following visits within six months. All the patients, who answered the questions of ASEX, filled in HADS also. Therefore, ASEX and HADS results of these 18 patients are given together in Table 3. Among these 18 patients, three (30%) patients using PROD and four (50%) patients using L/S were female. The average age of PROD group was 52.8±10.34 and of L/S group was 56.38±12.27 years. There was no significant difference between baseline and following highest ASEX scores whereas there was a significant decrement in the viral load. Women had higher ASEX scores (16.71±3.86) than men (12.18±3.37) (p=0.018, t=2.631) at the baseline assessment, although there was no significant difference in terms of gender during the treatment period. No correlation was detected between ASEX scores and age or viral load at the baseline assessment and during follow-up. Eight (61.5%) patients with sexual dysfunction at the baseline assessment also had anxiety risk. During the follow-up period, all the patients with anxiety risk and depression risk also had sexual dysfunction.

Eight patients using PROD and four patients using L/S filled the ASEX both at the beginning of the treatment and at the first month. Among these 12 patients, three (37.5%) patients using PROD and two (50%) patients using L/S were female. The average age of PROD group was 54.63±10.11 and of L/S group was 56±6.53 years. Comparison of their baseline scores with the first-month scores for ASEX is given in Table 4. As there were only four patients in L/S group, statistical analysis for the comparison between baseline and first-month measurements is made for the whole

group. All the patients with anxiety risk and depression risk at the first-month assessment had also sexual dysfunction. However, there was no correlation between ASEX scores and depression or anxiety scores neither at the baseline assessment nor at the first-month assessment.

Discussion

Health-care costs associated with hepatitis C (cirrhosis, cancer, transplantation) are increasing gradually over the years. Therefore, more effective, more tolerable, shorter and easier to use treatment regimens are needed. Today, DAAs replaced interferon and ribavirin treatment which had lower SVR with higher neuropsychiatric side effects (20,28). In our study, SVR was achieved in 85.7% of patients with a rapid drop in viral load in the first month of treatment. Consistent with the literature, virological failure was rare.

Our results are in line with the studies reporting that DAA treatment did not affect anxiety and depression scores (19,20). Although we used the highest depression or anxiety scores as following visit scores, we did not find any difference between baseline and following visit scores. Besides, consistent with the study of Gallach et al. (20) (2018), no significant differences were found in anxiety and depression scores when these variables were analyzed for age and gender. As depression was a leading side effect of interferon-containing treatments, most of the patients with psychiatric disorders could not get efficient treatments (10). DAAs seem to have a significant advantage over interferon-based treatments for psychiatric side effects. In a retrospective cohort study, it was found that Beck Depression Inventory scores improved with sofosbuvir-based treatment (29). DAAs are supposed to reduce extrahepatic manifestations such as fatigue and depression by reducing the systemic inflammation and immune activation secondary to HCV replication (30). However, in our study, we did not observe an improvement in depression or anxiety scores.

To our knowledge, there is no study which investigated the sexual effects of DAAs. In our study, we found that DAAs do not affect sexual scores of the patients. However, it is noteworthy that sexual dysfunction was found in around 75% of patients at the baseline assessment and around 95% during the follow-up period. This high prevalence may be related to HCV infection itself. In a review of Karaivazoglou et al. (24), sexual dysfunction prevalence was reported to be 19.4-88% in men and 48.7-79% in women. In a study from Turkey, sexual dysfunction was found to be in 35% of 111 sexually active, drug naive patients with HCV (31). Consistent with most of the studies investigating sexual dysfunction in HCV patients, we found a greater sexual impairment in female patients at the baseline assessment. There are contradictory results about the association between sexual functioning and psychiatric variables in patients with HCV infection. In our study, we did not find any correlation between sexual functioning scores and anxiety or depression scores. On the other hand, it is important that all the patients with anxiety disorder risk or depression risk also had sexual dysfunction during the follow-up period. We can interpret this finding as depression and anxiety disorders may have an additional effect on sexual dysfunction in HCV-infected patients during DAA treatment. Use of antidepressants and some other medications are also related to sexual dysfunction (32). As we do not know other medications of the patients, we cannot make an ultimate comment about this finding. Further studies on the sexual effect of DAA are needed.

Study Limitations

Our primary limitation is the small sample size which was limited to a single site. Secondly, due to the retrospective design of the study, we cannot rule out the potential bias related to the missing data about the previous history of mental disorders and used psychiatric medications. Although the patients with depression or anxiety disorder risk were referred to a psychiatrist, they did not apply to the consulted psychiatrist. However, they might get medical advice from another source. As we do not have information about patients' use of psychotropic medication, we could not make a further analysis by omitting the patients who had psychiatric treatment. This shortage leads to a significant limitation. On the other hand, this is reflective of a real-life setting, as psychiatric patients keep their illness (including substance abuse) as a secret mostly, in Turkey. Additionally, treatment adherence of the patients was not asked. Besides, there may be a significant difference between the patients who completed the questionnaires and who did not, in terms of psychiatric status. Also, our findings are limited to PROD and L/S regimens, which may not be generalizable to other DAA agents. Another major limitation is using only self-report questionnaires. Further prospective studies with structured or semi-structured interview supplying comprehensive clinical assessment will improve our knowledge. Lastly, data about other factors which can be related to psychiatric conditions such as anemia, hypothyroidism or vitamin B12 deficiency are missing.

Conclusion

Studies focused on psychiatric adverse effects of DAAs in the real world are lacking and one strength of this study is providing findings from routine clinical practice. Our results reinforce the evidence that DAAs are well tolerated and characterized by having no effect on anxiety, depression levels or sexual health of the patients. Further prospective studies with larger patient samples are needed to enhance our knowledge about the safety of DAAs in the psychiatric area.

Ethics

Ethics Committee Approval: We have obtained approval for the study from the Infectious Diseases and Clinical Microbiology Department of Ege University.

Informed Consent: Patients gave consent to the use of their data.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.K.T., M.I.T., Design: Ö.K.T., D.A., H.P., T.Y., M.I.T., Ö.Ö.S., Data Collection or Processing: Ö.K.T., D.A., Analysis or Interpretation: Ö.K.T., D.A., H.P., T.Y., M.I.T., Ö.Ö.S., Literature Search: Ö.K.T., D.A., H.P., T.Y., M.I.T., Ö.Ö.S., Writing: Ö.K.T., D.A.

Conflict of Interest: The authors claim that they have no conflict of interest.

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

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Case Report

Doi: 10.4274/vhd.galenos.2018-0029
Viral Hepatitis Journal 2019;25(1):32-34

Non-hodgkin Lymphoma Developing After Discontinuation of Direct-acting Antiviral Treatment for Hepatitis C: A Case Report

Hepatit C'nin Direk Etkili Antivirallerle Tedavisinden Sonra Gelişen Non-hodking Lenfoma: Bir Olgu Sunumu

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ABSTRACT

Today, direct-acting antivirals (DAA) are the main treatment options for hepatitis C infection. However, whether malignancy risk is increased after DAA treatment is a matter of debate. Conflicting results have been reported in the relevant studies. In this paper, we present the case of B-cell non-Hodgkin lymphoma developing after DAA treatment in a patient with complete response to hepatitis C treatment.
Keywords: Hepatocellular carcinoma, hepatitis C, non-Hodgking B cell lymphoma

ÖZ

Günümüzde doğrudan etkili antiviraller (DAA), hepatit C enfeksiyonu için ana tedavi seçenekleridir. Fakat DAA tedavilerinden sonra, hastalarda malignite riskinin arttığına yönelik olgu sunumları vardır. Konuyla ilgili araştırmalarda çelişkili sonuçlar bildirilmiştir. Bu sunumda DAA tedavisi sonrasında tam cevap elde edilen bir hastada tedaviden sonra gelişen B hücreli non-Hodgkin lenfoma ve arasındaki deneyimin paylaşılması amaçlanmıştır.
Anahtar Kelimeler: Karaciğer kanseri, hepatitis C, non-Hodking B cell lenfoma

Karabay O, Güçlü E, Hacıbekiroğlu T, Kösem M. Non-Hodgkin Lymphoma Developing After Discontinuation of Direct-acting Antiviral Treatment for Hepatitis C: A Case Report. 2019;25:32-34.

Introduction

The frequency of side effects associated with direct-acting antiviral (DAA) treatment is very low compared to interferon-based treatments (1). Currently, sustained virological response (SVR) has increased significantly with the use of DAA in hepatitis C treatment. More than 95% of patients have a SVR after DAA-based treatment (2). Moreover, even patients with decompensated cirrhosis may become treatable after treatment with DAAs.

The targeting of new antiviral drugs directly to hepatitis C virus (HCV) replication allowed very high response rates compared to old regimens, regardless of the stage of liver fibrosis. Currently, more than 95% of patients have a SVR after DAA-based treatment (2). However, there have been a few reports of occurrence of malignancy in patients previously treated with DAAs (3,4). In a multi-center study from Spain with 58 patients and in a single center study with 59 patient from Italy revealed that the incidence of hepatocellular cancer (HCC) was higher in patients treated with DAA (3,4). DAA treatment may also be associated with higher tumor recurrence rate. However, the validity of these data has not been confirmed in different studies (5). In this report, we aimed to present the case of B-cell non-Hodgkin lymphoma (BNHL) in a patient treated with DAA.

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Case

A 77-year-old woman has been followed up with chronic hepatitis C since 2009. She was previously treated with pegylated-interferon and ribavirin combination. Although the response was obtained by treatment, relapse was subsequently occurred. In March 2016, laboratory examinations showed a sedimentation rate of 44 mm/h, an alpha fetoprotein level of 9.29 ng/mL, alanine aminotransferase of 62 IU/L, HCV-RNA viral load of 1471602 IU/mL with genotype-1b and the patient was anti-HCV-positive. After relapse, we decided to treat the patient with DAA. The initial complete blood test (November 2016) revealed a hemoglobin level of 135 g/L (normal range: 115-150 g/L), a white blood cell (WBC) count of 6.86x109/L (normal range: 3.5-9.5x10^9/L) (neutrophil-69.4%, lymphocyte-23.9%, monocytes-5.82%), and a platelet count of 157x109/L (normal range: 125-350x109/L). After splenectomy (December 2017), the values were as follows: WBC: 7060 K/UL (neutrophil-60.8%, lymphocyte-28%, monocytes-9.58%), hemoglobin 11.6 g/L, and platelet 504 K/UL. Before treatment, there was no mass detected by abdominal ultrasonography (USG) (It was done at two times at 2016). She was treated with ombitasvir-paritaprevir-ritonavir and dasabuvir (OPRD) for 12 weeks in November 2016. HCV-RNA became negative after the first month of OPRD treatment. SVR was obtained 12 weeks after the treatment.

In June 2017, the patient suffered from fatigue and feeling of fullness and pain in the upper left quadrant. A splenic mass (9x7 cm) was detected USG in the spleen six months after cessation of the treatment (Figure 1).

In June 2018, surgical resection of the splenic mass was done. Histological analysis of the surgical specimen revealed high-grade B-cell NHL. The patient, who is still being followed up in our clinic was cured after three cycles of chemotherapy (R-CHOP chemotherapy protocol) followed by radiotherapy. Written informed consent was obtained from the patient.

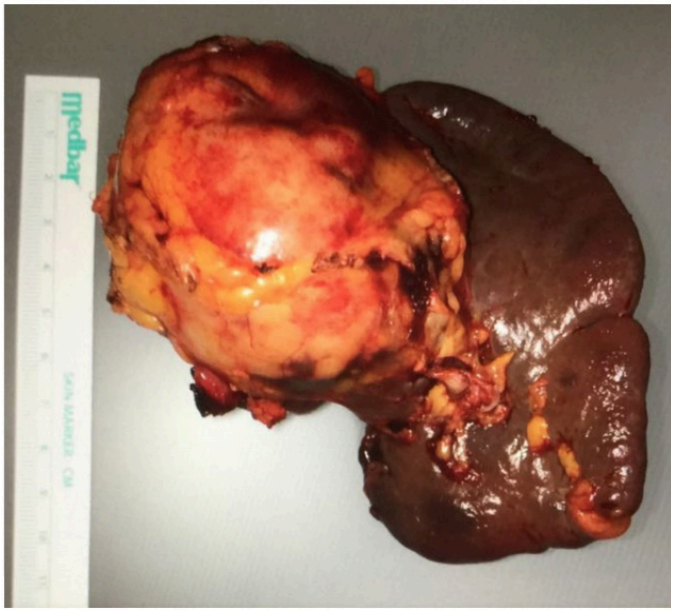

Figure 1. The splenic mass

Discussion

HCV is a lymphotropic and hepatotropic virus affecting nearly two hundred million people in the world (6,7). We clearly know that BNHL is related with HCV infection. HCV infection has been reported in nearly 13% of patients with BNHL (8). Chronic antigenic stimulation of the immune system by HCV infection may lead to BNHL. A very similar situation applies to *Helicobacter Pylori.* MALP lymphoma develops as a result of similar pathology in *H. Pylori* infections (9). T cell-dependent responses are also involved in the pathogenesis of this event. We think that it is very important to decrease the antigenic concentration in the development of malignancy. In addition, we conclude that with the termination of antigenic stimulation, there is a decline in immunity, thus developing lymphoma in an immune organ such as the spleen.

In our case, there was no evidence of malignancy before treatment. However, the development of lymphoma after months of therapy and SVR was interpreted as a lack of immune stimulation. A period of 6-7 months after treatment can be considered as a very short period for the development of lymphoma. However, the fact that there was no mass in the spleen detected by USG before treatment suggests that this condition was related to HCV treatment.

A similar situation applies to HCC. The probability of HCC relapse following DAA in HCV infection treatment is still unclear. The role of the immune system before and after tumor development is very important. HCV-infected liver cells are constantly alerted by the immune system. If infected cells are destroyed, the efficacy of the immune system in the liver is significantly reduced. In some studies, it has been shown that DAA treatment affects natural killer cells (10). In their study, Chu et al. (11) reported that after DAA treatment, a rapid decrease was seen the level of natural killer group 2, member D protein (NKG2D) which is relased from natural killer cells. The low level NKG2D was correlated with early HCC emergence in DAA-treatment.

Two different study reported increased HCC after complete response to DAA therapy in patients with HCV (3,4). At this point, the disorder that occurs in the release of these substances may be accelerating the oncogenic process. Virus-induced inflammation may play an important role in chronic liver injury and in the onset of the tumor development in chronic hepatitis (12). However, at the same time, the immune system is necessary to prevent tumor formation (13). Again, as long as there are cells that are infected with HCV, the immune system is also actively working to destroy these cells. If HCV clearance occurs, the immunosuppressive effect of the system (both for virus-infected cells and tumor cells) is degraded. Immune regression also accelerates tumor development.

Lastly, we think that the risk of cancer in patients receiving DAA suggests that these patients should be monitored closely after therapy is completed.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.K., Concept: O.K., Design: E.G., Data Collection or Processing: O.K., E.G., Analysis or Interpretation: T.H., M.K., Literature Search: O.K., E.G., Writing: O.K., E.G., T.H., M.K.

Conflict of interest: The authors declare that they have no conflict of interest.

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

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