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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.
The journal's editorial policies are based on "ICMJE Recommendations" (2016, http://www.icmje.org/) rules.
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INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

Viral Hepatitis Journal (Formerly Viral Hepatit Dergisi) is an independent, peer-reviewed international journal published quarterly in April, August, December. The official language of the journal is English.

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.

Viral Hepatitis Journal does not charge any article submission or processing charges. Any processes and submissions about the journal can be made from the website: http://viralhepatitisjournal.org/. Past issues of the journal are also available at this website. Manuscripts should submitted online from https://mc04.manuscriptcentral.com/viralhepatj.

The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can be done at http://orcid.org.

In the international index and database, the name of the journal has been registered as Viral Hepatitis Journal and abbreviated as Viral Hepat J.

SCIENTIFIC POLICIES

Scientific and Ethics Responsibility

The author(s) undertake(s) all scientific responsibility for the manuscript. All the authors must actively participate in the study. The author(s) guarantee(s) that the manuscript itself or any substantially similar content of the manuscript has not been published or is being considered for publication elsewhere. If the manuscript had been presented in a meeting before; the name, date and the province of the meeting should be noted.

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/).

The authors should acknowledge and provide information on grants, contracts or other financial support of the study provided by any foundations and institutions or firms.

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.

In case of retraction of the text by author(s) for any reason again needs a written and signed application explaining the reasons.

The name of the institution where the authors work and the name of the institution or the department in which the study has been conducted should not be mentioned in the submitted manuscript.

The corresponding author must give the full corresponding address (including telephone, fax number and e-mail address). Contact information for corresponding author is published in the journal.

The authors should keep a copy of the submitted manuscripts and other documents.

If the whole or a part of the submitted manuscript needs to be published somewhere else, Editorial Office must be informed accordingly.

Review Process: Upon submission, all manuscripts are reviewed to check for requirements requested by the Journal. Manuscripts that do not comply with these requirements will be sent back to authors without further evaluations. All the papers are first evaluated by the editor; later the papers are sent to advisory board members. If needed, some questions can be asked to the authors to answer; or some defaults may have to be corrected by the authors.

The result can be acceptance, minor revision, major revision, rejection in the current form, or rejection. Accepted manuscripts are forwarded for publication; in this stage, all information and data are checked and controlled properly; the proof of the article to be published by the journal are forwarded to the writers for proof reading and corrections.

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The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2016, archived at http://www.icmje.org/).

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/),

STROBE statement—checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/),

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

MANUSCRIPT PREPARATION

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

• Research articles and article collections should not exceed 15 pages including the text, figures, tables and references, while short announcements and case report presentations should not be longer than 5 pages.

Short Announcements

i. Turkish title, English title, author name 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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• Author number for case report presentations should not exceed four.

• 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.

Manuscripts should have double-line spacing, leaving sufficient margin on both sides.

Manuscripts should be written with Microsoft Word.

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.

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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.

Materials and Methods: **The study and standard criteria used should be defined; it should also** be indicated whether the study is randomized or not, whether it is retrospective or prospective, and the statistical methods applied should be indicated, if applicable.

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.

Keywords:

• They should be minimally 3 and maximally 6 and should be written in Turkish and English.

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

• English key words should be appropriate to "Medical Subject Headings (MESH)" (www.nlm.nih.gov/mesh/MBrowser.html).

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

Original researches should have the following sections;

Introduction: Should consist of a brief explanation of the topic and indicate the objective of the study, supported by information from the literature.

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.

References: Authors are responsible for the accuracy of the references. See General Guidelines for details about the usage and formatting required.

Case Reports

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 key words. 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).

Review Articles

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.

Reviews articles analyze topics in depth, independently and objectively. The first chapter should include the title in Turkish and English, an unstructured summary and key words. Source of all citations should be indicated. The entire text should not exceed 25 pages (A4, formatted as specified above).

Letters to the Editor

Letters to the Editor should be short commentaries related to current developments in viral hepatitis and their scientific and social aspects, or may be submitted to ask questions or offer further contributions in response to work that has been published in the Viral Hepatitis Journal. Letters do not include a title or an abstract; they should not exceed 1,000 words and can have up to 5 references.

References: The authors are required to cite only those references that they can submit to the Journal in the event they are requested to do so. References should be cited in numerical order (in parentheses) in the text and listed in the same numerical order at the end of the manuscript on a separate page or pages. All authors should be listed regardless of number. Journal abbreviations should conform to the style used in the Cumulated Index Medicus (www.icmje.org). Only list the literature that is published, in press (with the name of the publication known) or with a doi number in references. It is preferred that number of references do not exceed 50 for research articles, 100 for reviews and 10 for case reports.

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).

Format for journal articles; initials of author's names and surnames, titles of article, journal name, date, volume, number, and inclusive pages, must be indicated.

Example: Tabak F, Ozdemir F, Tabak O, Erer B, Tahan V, Ozaras R. Autoimmune hepatitis induced by the prolonged hepatitis A virus infection. Ann Hepatol. 2008;7:177-179.

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

Example: Vissers RJ, Abu-Laban RB. Acute and Chronic Pancreatitis. In: Tintinalli JE, Kelen GD, Stapczynski JS (eds.), Emergency Medicine: A comprehensive Study Guide. 6 st ed. New York: McGraw-Hill Co; 2005; p. 573-577.

Format for on-line-only publications; DOI is the only acceptable on-line reference.

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Explanations about figures, pictures, tables and graphics must be placed at the end of the article.

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Acknowledgment: Only acknowledge persons and institutions who have made substantial contributions to the study, but was not a writer of the paper.

All manuscripts submitted to the Viral Hepatitis Journal are screened for plagiarism using the "Crossref Similarity Check powered by iThenticate" software. Results indicating plagiarism may result in manuscripts being returned or rejected.

Checklist for Submitted Articles:

Articles must be complete. They must include the following:

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• Title Page

• Article sections

• Turkish and English titles

• Abstract (250 words) (Turkish and English)

• Keywords (minimum 3; maximum 6)

• Article divided into appropriate sections

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• "Copyright Form" signed by all authors.

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CONTENTS

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Which One Should Be Prefered: Liver Biopsy or Non-Invasive Procedures?

Hangisi Tercih Edilmelidir: Karaciğer Biyopsisi mi Non-İnvazif Testler mi?

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In this recent issue of Journal of Viral Hepatitis, Karacaer et al. (1) aimed to evaluate the percutan liver biopsy safety. Liver biopsy has currently some major roles that are diagnosis, assesment of prognosis (especially staging of parenchymal liver diseases) and deciding of therapy. It is seen as the gold standard according to current clinical practice. Because of its some restrictive and limiting features and some complications, several non-invasive methods have been developed (2).

Percutaneous liver biopsy has a risk of complication and mortality; 1-5%, 0.009-0.01% respectively. In addition; the other disadvantages are sampling error, at least 6-24 hours of monitoring in hospital, difficulties in follow-up treatment, and high cost. Karacaer et al. (1) found that 71% of patients had complaints (mostly pain) and 19.9% developed complications but no mortality occurred at this multicenter study. They noted that biopsy methodology and patient-specific factors are not related with the post biopsy pain but biopsy needle type and physician-specific factors.

Prebiopsy and peribiopsy patient preparations are very important for prevention of some complications during percutan liver biopsy. The patient should be informed about this procedure's details. Cooperation of patient is important issue for successfull procedure. The major complications are pain and bleeding. After biopsy, patient should be monitored closely.

Non-invasive procedures are also recommended as an alternative to liver biopsy for the purpose of determining the severity of liver disease and deciding for treatment in chronic viral hepatitis. According to the last European Association for the Study of the Liver guideline, evaluation of liver disease severity is the mainstay of the therapy indication (3). As liver biopsy which demonstrates only 1/50.000 of liver parenchyma and the evaluation may be varied according to the pathologist's eye, the strength of the histopathologic assessment of disease severity may not be perfect. Moreover, it may be necessary to repeat the procedure for monitoring the response of the treatment. There are many non-invasive diagnostic methods. Although the sensitivity, specificity and diagnostic accuracy rates of these methods are quite high, liver biopsy is still gold standart for assessment of liver disease severity. However, the combination of non-invasive tests enhances the sensitivity of these tests (4). Therefore, their use may reduce the need for biopsy which has several complications.

Güner R. Baykan N. Which One Should be Prefered: Liver Biopsy or Non-Invasive Procedures? Viral Hepat J. 2017;23;1-1.

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Research Article

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Doi: 10.4274/vhd.0001
Viral Hepatitis Journal 2017;23(3):65-70

Percutaneous Liver Needle Biopsy Methods Can Be Safe and Effective in Patients with Viral Hepatitis

Viral Hepatit Hastalarında Perkutan Karaciğer İğne Biyopsi Yöntemleri Güvenli ve Etkindir

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ABSTRACT

Objectives: The aims of this study were to evaluate the biopsy methods used in terms of safety, and effectiveness as well as incidence, and severity of complications.

Materials and Methods: This study was conducted as a prospective, observational study with the participation of five centers in Turkey. Any patient complaints and/or complications were also recorded. The patients' pain severity was determined by an established scoring method.

Results: This research included 221 chronic hepatitis patients and 12 physicians. With regard to the biopsies, 71.9% were ultrasound-guided and 28.1% were blind biopsies. 71% of patients had complaints (mostly pain) and 19.9% developed complications; however, no mortality occurred. It was observed that patient's complaints were significantly correlated with the physician's age, level of biopsy experience, and number of biopsies performed yearly. It was determined that the biopsy method was not affective factor in terms of the development of severe pain after biopsy. The use of a 16G biopsy needle was found to increase the probability of severe pain occurrence by about eight times.

Conclusion: Severe pain was not affected by the biopsy method or patient-specific factors, and was a result of the size of the biopsy needle used and the characteristics of the practitioner.

Keywords: Liver, viral hepatitis, biopsy, complication

ÖZ

Amaç: Bu çalışmada karaciğer biyopsi yöntemlerinin güvenilirliği, etkinliği ve komplikasyonların şiddetinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu araştırma Türkiye'de beş merkezin katılımıyla prospektif ve gözlemsel olarak gerçekleştirilmiştir. Hastaların şikayetleri ve/veya komplikasyonlar kaydedilmiştir. Hastaların ağrı şiddeti puanlama yöntemi ile belirlenmiştir.

Bulgular: Çalışmaya 221 kronik viral hepatit hastası ve 12 hekim katılmıştır. Biyopsilerin %71,9'u ultrasonografi eşliğinde, %28,1 kör biyopsi yöntemi ile yapılmıştır. Hastaların %71'inde şikayet (çoğunluğu ağrı) ve %19,9'unda komplikasyon gelişmiştir. Ancak mortalite gözlenmemiştir. Biyopsiyi yapan hekimin yaş grubu, biyopsi deneyim süresi ve yıllık biyopsi sayısı ile şikayetlerin oluşması arasında anlamlı ilişki saptanmıştır. Biyopsi sonrası şiddetli ağrı gelişimi açısından biyopsi yönteminin etkili bir faktör olmadığı belirlenmiştir. Şiddetli ağrı varlığını 16G biyopsi iğnesi kullanmanın yaklaşık sekiz kat arttırdığı saptanmıştır.

Sonuç: Şiddetli ağrının biyopsi yöntemi veya hastaya özgü faktörlerden etkilenmemekte, kullanılan biyopsi iğnesi ve uygulayıcının özelliklerinden kaynaklanmaktadır.

Anahtar Kelimeler: Karaciğer, viral hepatit, biyopsi, komplikasyon

Karacaer Z, Yılmaz Karadağ F, Durmuş G, Çiçek H, Parlak E, Arı A, Tosun S, Durmuş Y, Eren S, Adıbelli Z. Percutaneous Liver Needle Biopsy Methods Can Be Safe and Effective in Patients with Viral Hepatitis. Viral Hepat J. 2017;23:64-70.

This study was presented as a poster presentation in XVIII. Turkish Infectious Diseases and Clinical Microbiology Congress, Antalya, 2017

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Introduction

Liver biopsies are necessary in the diagnosis of parenchymal liver diseases, monitoring disease progression, and/or treatment decisions. Although several noninvasive methods have been introduced recently, a liver biopsy still provides the best results. Tissue samples required for histopathological investigations can be obtained by either imaging-guided or blind biopsy methods. The blind biopsy methods include percutaneous needle, transvenous (transjugular), laparoscopic or open wedge (surgical) biopsies. Imaging-guided biopsy is performed in order to provide visual control in the diagnosis of a focal lesion in the liver. For this method, ultrasonography (USG) is usually preferred, while computed tomography is rarely utilized (1).

Biopsy is contraindicated in patients with a history of extrahepatic biliary obstruction, bacterial cholangitis, coagulation disorders, ascites, cystic lesions, and amyloidosis, as well as in uncooperative patients (2). In order to perform a liver biopsy, the platelet count should be higher than 60.000/μL, the prothrombin time (PT) should be shorter than 4 seconds, the international normalized ratio (INR) value should be lower than 1.4, and the activated partial thromboplastin time (APTT) should not exceed 1.5 times the reference value. Therefore, performing a full blood count and coagulation analysis, and ruling out focal lesions within the liver with imaging methods are recommended before performing a biopsy (1).

Despite taking precautionary measures, the rates of biopsy-related morbidity and mortality range from 0.08 to 0.34% and from 0 to 0.19%, respectively (3). Cooperation status of the patient, advanced age, bleeding disorders, presence of underlying diseases (such as cirrhosis, ascites, or malignancy), biopsy experience of the person performing the biopsy, biopsy method used, diameter of the biopsy needle, and type and number of interventions are the factors most affecting the development of complications (4). The most common complication observed following a liver biopsy is mild pain felt in the biopsy area and the right shoulder. Severe pain in the abdomen may be indicative of serious complications, such as intra-abdominal hemorrhage or peritonitis (3). In addition, the following conditions may develop: major or minor bleeding, pneumothorax, hemothorax, organ perforation, bile peritonitis, infection, hemobilia, intrahepatic arteriovenous fistula, or neuralgia. In general, major complications requiring hospitalization occur within the first three hours after biopsy (4).

The objectives of this multicenter study were to determine the risk factors related to liver biopsy with prospective observations, and to evaluate two different biopsy methods (USG-guided and blind) in terms of safety and effectiveness as well as incidence and severity of complications.

Materials and Methods

Study Design and Features of the Study Group

This was a prospective, observational study conducted between July 1, 2015 and September 1, 2016, with the participation of five centers in Turkey. It consisted of patients, who presented to the infectious diseases and clinical microbiology clinics due to viral hepatitis and were scheduled for liver biopsy. Needle biopsies were performed by physicians in attendance at the infectious diseases and clinical microbiology and radiology clinics.

The patients' demographics, medical history, liver disease information, biopsy method, the type of needle used, complaints, complications, treatment administered after the biopsy, histopathological outcomes, characteristics of the pain felt, and follow-up information were recorded. Demographic characteristics and information about the liver biopsy experience of the physicians who performed the liver biopsies were also included in the data set.

Liver Biopsy

Each patient underwent a complete blood count and coagulation test to rule out any contraindication before the liver needle biopsy. Any medications or drugs that can cause coagulation disorders were discontinued before the biopsy. In patients with existing coagulation disorders, the liver biopsy was planned after they underwent proper treatment. Either a USG-guided or blind biopsy was performed under local anesthesia with a 14–18 gauge (G) needle. The liver parenchyma was assessed using the modified Knodell scoring system (Ishak) in the pathology laboratory of the relevant center. Patients with a histology activity index (HAI) between 0 and 7 were defined as mild, with the others having severe activity; those with a fibrosis score from 0 to 2 were considered to have mild fibrosis, with the others defined as severe.

Biopsy Complications

The patient's complaints were registered, and the clinical symptoms, blood pressure, and pulse were recorded in the clinic after the biopsy, with a full blood count ordered after two hours. Following the liver biopsy, any mild-to-severe pain, major or minor bleeding, pneumothorax, hemothorax, organ perforation, bile peritonitis, infection, hemobilia, and/or intrahepatic arteriovenous fistula development were defined as complication (4). A 4% reduction in the hematocrit control was defined as bleeding; this was considered to be minor if intervention was not necessary, and major if treatment was needed. For the blood pressure, a level lower than 90/60 mmHg, or a 20 mmHg or higher drop in the systolic blood pressure and a 15 mmHg or higher drop in diastolic blood pressure (compared with the pre-biopsy levels) were diagnosed as hypotension (5).

To determine pain severity, the patients were asked to report their pain numerically: no pain=0, intolerable pain=10, and the other pain severities were rated between 1 and 9 points (6). Any pain reported as six or higher was defined as "severe pain." Both the type of pain and the location were recorded at the 2nd and 24th hours after the liver biopsy, and at the time of presentation for the first follow-up examination.

Inclusion and Exclusion Criteria

Those patients and physicians who provided written consent were included in this research. In addition, pre-cirrhotic/cirrhotic patients using antiviral therapy (continued/stopped) were included in the study. However, patients who refused to participate, those under 18 years of age, and those in whom post-biopsy follow-ups could not be performed, as well as physicians who did not provide consent were excluded from the study.

Ethical Issues

The Declaration of Helsinki and Good Clinical Practice Guidelines were respected during the entire process of enrolling the patients in

the study and collecting/analyzing/reporting the data. This research was approved by the Istanbul Medeniyet University, Göztepe Training and Research Hospital Ethics Committee (01.07.2015-2015/0090).

Statistical Analysis

The study data was transferred to the SPSS IBM 22.0 statistical program (SPSS Inc., Chicago, IL, USA) in order to perform the data control and analysis. The distribution of the data was evaluated using the Kolmogorov-Smirnov test. The descriptive data was shown as the frequency distribution and percentage, while the non-normally distributed data was expressed as the median (minimum-maximum).

The patients were grouped according to the biopsy methods, needle diameters, physicians' age groups, physicians' biopsy experience, and the physicians' academic degree and number of biopsy per year. The complaints, complications, and features of the liver materials were also analyzed. The categorical variables were compared using Pearson's chi-squared and Fisher's exact tests. The continuous variables were assessed using the Mann-Whitney U and Kruskal-Wallis tests. A binary logistic regression analysis was used in the multiple analyses and a p value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics

This research included 221 chronic viral hepatitis patients, with an 86.4% naivety rate. Of these patients, 67% were males and the median age was 36 (18–83) years. Liver biopsy was performed in 93.7% of patients due to e hepatitis B virus (HBV) infection, 5.4% due to hepatitis C virus (HCV) infection, and 0.9% due to HBV-HCV coinfection. The median duration of the patients' knowledge of their chronic viral hepatitis was 6 (1–37) years.

It was determined that 20.4% of patients had another chronic disease; 75.5% of patients with other chronic diseases used various drugs for these diseases and 3 patients used anticoagulant drugs. Of the patients included in this study, 26.7% had previously undergone liver biopsy and 22% had developed complications; the most common complication was severe pain (92.3%). No coagulation disorders were observed in any of the patients.

Characteristics of the Physicians Who Performed the Biopsies

Out of the 12 physicians who participated, 81.9% were males, and the median age was 46 (26–52) years. The median service duration in the field of specialization of the physicians was 5 (3–26) years, the median liver biopsy experience was 4 (<0–23) years, and the median number of liver biopsy per year was 75 (20–240). Of the physicians, 71.9% were radiologists and 28.1% were infectious diseases specialists. Moreover, 48.4% of the biopsies were performed by specialists, 33% by assistants/research assistants, and 18.6% by chief assistants/academicians.

There was a significant difference when the physicians' yearly biopsy numbers and level of biopsy experience were compared according to their titles (p<0.001). It was determined that those physicians who performed biopsies most frequently in one year were assistants/research assistants, and those with an experience of 6 years or longer were specialists. Although the number of biopsy per year was higher than 50 for all the assistants/research assistants, their experience was determined to be less than one year.

Liver Needle Biopsy Outcomes and Related Factors

With regard to liver biopsies, 71.9% were USG-guided and 28.1% were blind biopsies. The USG-guided biopsies were performed for the following reasons: 62.3% because of the clinical protocol, 32.1% because it was thought to be safer, 3.8% due to obesity, 1.3% due to narrowing in the intercostal space, and 0.6% due to old age. 16G biopsy needles were used in 67.9% of the cases, 18G in 23.5%, 14G in 5.9%, and 17G in 2.7%. Tru-Cut needles (67.9%) and automatic biopsy needles (32.1%) were used in USG-guided biopsies, and Menghini needles were used in blind biopsies.

In the histopathological outcomes, the median HAI value was 6 (0–17) and the median fibrosis value was 1 (0–5). Mild histological activity (75.6%) and fibrosis (75.1%) were detected in the majority of patients; however, no cirrhotic patients were seen in this study. Insufficient material was obtained from 11 patients; nine with USG-guided and two with blind biopsies. No significant correlation was found between obtaining insufficient material and the biopsy method or needle diameter (p=0.524 and p=0.271, respectively). A similar situation was observed in the characteristics of the biopsy physician, and no significant correlation was found between obtaining insufficient material and the age group, level of biopsy experience, or title of the physician (p=0.368, p=1.00, and p=0.503, respectively). There was a positive correlation between the length of the liver material and the number of portal areas (r=0.281, p<0.001).

Post-biopsy Complaints, Complications, and Related Factors

Following the liver biopsy, the median duration to the follow-up on the first day was 6 (3–48) hours. The median duration to the next follow-up day after the biopsy was 21 (5–90) days. Of the patients, 71% reported complaints: 76.5% had headache, 6.8% had shortness of breath, 3.2% felt dizziness, 2.3% had nausea, 1.8% felt fatigue, 0.5% had palpitations, and 2.3% reported other complaints.

After the liver biopsy, 19.9% of patients developed complications, including severe pain (97.7%) and hypotension (2.3%). The pain was felt in the liver region in 60.6%, in the right shoulder in 25.8%, around the abdomen in 4.5%, and in other regions (headache in 1 patient, lower back pain in 1 patient) in 0.9% of the patients. In addition, 12.2% reported that they received non-narcotic analgesics because of pain.

The most common complaints of any type following the biopsy occurred inpatients ≤30 years old (p=0.001). However, no significant correlation was found between the complaints and the patients' gender, HAI, fibrosis level, type of hepatitis, or presence of another chronic disease (p=0.5, p=0.826, p=0.292, p=0.222, and p=0.056, respectively). The complaints were experienced more commonly after the blind biopsy procedure, and with the use of a 16G needle (p<0.001 and p=0.007, respectively) (Table 1). There

was a significant correlation between the occurrence of complaints and the physician's age group, level of biopsy experience, and the number of biopsy/year (p=0.046, p<0.001, and p<0.001, respectively) (Table 2).

It was found that the biopsy management, patient's age and gender, HAI and fibrosis levels, type of hepatitis, and presence of another chronic disease were not affective in terms of the development of severe disease after biopsy (p=0.464, p=0.328, p=0.516, p=0.845, p=0.783, p=0.162, and p=0.274, respectively). In addition, no significant correlation was observed between the development of severe pain and diameter of the needle used (p=0.322). In USG-guided biopsies, severe pain developed after biopsy in 27.6% of patients in whom 16G needles were used (p=0.001). Regardless of the method, severe pain was observed most frequently after the use of a 16G needle (p=0.001) (Table 1). In addition, it was observed that age and title of the physician who performed the biopsy affected the development of severe pain (Table 2).

The results of the multiple regression analysis did not reveal any risk factor that would affect the presence of a complaint. However, the use of a 16G biopsy needle was found to increase the presence of severe pain by about eight times [B=2.1, p=0.007, Exp. (B)=8.167].

Discussion

In this study, life-threatening complications did not develop after liver biopsy. However, severe pain and hypotension were observed in 19.9% of patients. This rate is higher than in other studies (7,8). Since this study was a prospective and observational study, we think that we follow patients more closely and question the existence of pain more rigorously. Therefore, complications may be more frequently observed.

Mortality after liver biopsy is very rare (7,8,9,10). After biopsy, pain and bleeding are the most common complications (7,8,9). A population-based study in Canada reported that 4275 percutaneous liver biopsies were performed on 3627 patients over nine years and only 32 (0.75%) patients developed significant complications. It was also reported that mortality developed in six patients (0.14%) and the most frequent complications were pain and bleeding requiring hospitalization. The cause of mortality was massive bleeding in five patients and aspiration pneumonia and congestive heart failure in the other patient (11).

Pain is the most common complication after liver biopsies (7,8,9). Similarly, in this study, the most common complication was severe pain. The mechanism of post-biopsy pain is often not clearly explained. Most likely, however, pain occurs after bile leakage from the biopsy line or capsular swelling after bleeding. There may also be pain transmitted from the skin or the liver capsule or both. Generally, pain begins as viscerosomatic pain in the right shoulder, peaks and disappears with pain in the biopsy area (3,4). The frequency and severity of pain decreases deliberately within 24 hours of maximum level in the first 30 minutes (12). In this study, the pain observed in the biopsy area was lasting on average two days.

Table 1. Distribution of the complications by biopsy method and biopsy needle diameter

	Blind biopsy (n=62)		USG-guided biopsy (n=159)			Needle diameter								
						14G (n=13)		16G (n=150)		17G (n=6)		18G (n=52)		
	No	Yes	No	Yes	p value[a,b]	No	Yes	No	Yes	No	Yes	No	Yes	p value[a,b]
Presence of complaints	0	62	64	95	<0.001	4	9	36	114	0	6	24	28	0.007
Presence of severe pain	48	14	130	29	0.464	12	1	110	40	6	0	50	2	0.001
	Median	min-max	Median	min-max	p value[a,c]	Median	min-max	Median	min-max	Median	min-max	Median	min-max	p value[a,d]
Tissue length (mm)	200	1-970	15	4-45	<0.001	24	13-45	20	1-970	26	12-46	20	10-40	0.879
Portal area number	9	3-41	8	1-30	0.056	15	10-30	8	3-41	15	10-30	7	1-19	<0.001
1. Pain score	4	0-10	2	0-10	0.001	2	0-10	3	0-10	1	0-2	2	0-10	<0.001
2. Pain score	2	0-7	0	0-7	0.006	0	0-5	1	0-7	0	0	0	0-6	0.001
3. Pain score	0	0-3	0	0-2	0.035	0	0	0	0-3	0	0	0	0-2	0.944
Total pain duration (days)	2	0-15	1	0-21	<0.001	0	0-1	1	0-15	0	0	1	0-21	<0.001

USG: Ultrasonography, 1. pain score: 2nd hour after biopsy, 2. pain score: 24th hour after biopsy, 3. pain score: First day of follow-up after biopsy, G: Gauge, min: minimum, max: Maximum [a]<0.05 statistically significant [b]Pearson's chi-squared and Fisher's exact tests [c]Mann-Whitney U test [d]Kruskal-Wallis test

Table 2. Distribution of complications by the characteristics of the physicians who performed the biopsies

	Age groups (years)					Biopsy experience duration (years)					Academic degree						Yearly biopsy number								
	≤40 (n=92)		≥41 (n=129)		p value[a,b]	≤5 (n=137)		≥6 (n=84)		p value[a,b]	Ass/Re Ass (n=73)		Specialist (n=107)		Chief Ass/ Aca (n=41)		p value[a,b]	≤50 (n=75)		51-100 (n=86)		≥101 (n=60)		p value[a,b]
	No	Yes	No	Yes		No	Yes	No	Yes		No	Yes	No	Yes	No	Yes		No	Yes	No	Yes	No	Yes	
Presence of complaints	20	72	44	85	0.046	54	83	10	74	<0.001	27	46	23	84	14	27	0.057	4	71	35	51	25	35	<0.001
Presence of severe pain	64	28	114	15	<0.001	108	29	70	14	0.412	47	26	91	16	40	1	<0.001	60	15	73	13	45	15	0.329
	Median	min-max	Median	min-max	p value[a,c]	Median	min-max	Median	min-max	p value[a,c]	Median	min-max	Median	min-max	Median	min-max	p value[a,d]	Median	min-max	Median	min-max	Median	min-max	p value[a,d]
Tissue length (mm)	20	1-500	20	4-970	0.531	16	4-45	150	1-970	<0.001	15	4-30	60	1-970	15	7-46	<0.001	180	1-970	16	5-40	15	4-40	<0.001
Portal area number	8	3-27	8	1-41	0.612	7	1-30	8	3-41	0.068	4	4-6	8	1-41	10	6-30	<0.001	10	3-41	6	1-19	8	6-13	<0.001
1. Pain score	3	0-10	2	0-10	0.175	2	0-10	3	0-10	0.002	3	0-10	3	0-10	2	0-10	0.282	3	0-10	2	0-10	3	0-10	0.015
2. Pain score	1	0-7	0	0-7	0.223	0	0-7	1	0-7	0.023	1	0-7	1	0-7	0	0-5	0.027	1	0-7	0	0-6	1	0-7	0.202
3. Pain score	0	0-2	0	0-3	0.494	0	0-2	0	0-3	0.124	0	0	0	0-3	0	0	0.115	0	0-3	0	0-2	0	0	0.189
Total pain duration (days)	1	0-10	1	0-21	0.371	1	0-21	1	0-15	0.001	1	0-7	1	0-21	0	0-7	<0.001	1	0-15	1	0-21	1	0-7	0.124

Ass/Re Ass: Assistant/research assistant, Chief Ass/Aca: Chief assistant/academician, 1. Pain score: 2nd hour after biopsy, 2. Pain score: 24th hour after biopsy, 3. Pain score: First day of follow-up after biopsy, min: Minimum, max: Maximum [a]<0.05 statistically significant, [b]Pearson's chi-squared and Fisher's exact tests, [c]Mann-Whitney U test, [d]Kruskal-Wallis test

Eisenberg et al. (12) found a correlation between anxiety before a biopsy and the pain felt within the first 6 hours following the biopsy. In addition, Akay et al. (13) reported that the pain expectations of patients were high before a liver biopsy, but they felt less pain than expected during the procedure. Therefore, the presence and/or severity of pain felt after biopsy that we found in our study might be associated with the anxiety levels of the patients.

In our study, the method used did not affect the occurrence of severe pain. However, in a previous study conducted on HCV patients, the pain and related morbidity following a blind biopsy were found to be more common than in USG-guided biopsy (14). Nevertheless, there are studies showing that whether or not biopsies are performed with USG guidance makes no difference in terms of development of complications (15).

When the factors related to pain were examined, severe pain was observed more commonly after biopsies performed by young physicians and assistants/research assistants. This result could be explained by the fact that the majority of the assistants/research assistants were under 40 years of age.

In our study group, a physician's level of experience and the number of biopsy per year did not affect the development of pain. In one previous study evaluating the complications that developed following blind biopsies, it was found that less physician experience was significantly correlated with a higher rate of procedure failure, but the level of experience did not influence the development of complications (9). Chevallier al. (16) reported that the level of experience made no difference in terms of pain severity following USG-guided liver biopsies.

Similar studies have shown that the factors affecting complications were severe fibrosis (9), performing three or more interventions, female gender, the presence of malignancy, and an INR of ≥1.4 (8). In our patient group, no correlation was found between pain and the level of fibrosis, gender, or the presence of chronic disease. Since our study did not include patients with coagulation disorders, INR levels were not evaluated.

Although no significant correlation was found between the biopsy methods and occurrence of severe pain, the average pain felt was higher and the mean duration of pain was longer with blind biopsies at the 2nd and 24th post-biopsy hours. It is believed that this result might be associated with the negative pressure created by the Menghini biopsy needles. Any patient undergoing a blind biopsy should be more closely followed-up in terms of pain severity.

No bleeding was observed in the study group. A large portion of the major complications are expected to develop within the first few hours after a biopsy (4). However, 70% of bleedings have been reported to develop after 24 hours (10), and last endup to 15 days (4). We believe that no bleeding complications were missed, since we followed up the patients for an average of 21 days after biopsy.

Factors that affect bleeding include a decreased platelet count and increased PT, INR, or APTT (5,17). Terjung et al. (10) reported the factors increasing the risk of bleeding as the following: mycobacterial infection [Odds ratio (OR): 24.0], pre-biopsy prophylactic platelet substitution (OR: 9.9), acute liver failure (OR: 9.1), heparin administration on the day of the biopsy (OR: 8.7), advanced liver cirrhosis (OR: 5.1), therapy with corticosteroids (OR: 3.5) or metamizole (OR: 2.8), and leukemia or lymphoma (OR: 2.8).

Since the patients in our study did not have these specified risk factors, no bleeding was observed after biopsies.

In this study, significant correlations were determined between liver tissue length and biopsy method, and between the number of portal sites and diameter of the needle used. However, the biopsy method and diameter of the needle used did not create a significant difference in terms of obtaining sufficient material for the pathological evaluation. Therefore, we believe that it may be misleading to evaluate the efficacy of the biopsy needle by the tissue length and number of portal sites. However, the experience of the physician was found to be important in terms of the tissue length and number of portal sites included in the liver biopsy (16). In our study, biopsy experience was also found to be associated with the tissue length.

The present research contributes to the scarce number of studies that have been prospectively designed. Retrospective studies remain weak in accurately reporting the presence and severity of a subjective complication, such as pain. We believe that the data obtained from our study could be passed on to the patients to inform them on the possibility of complications that could occur after a biopsy, as well as the severity, duration, and location of the pain before the biopsy.

Study Limitation

Unlike retrospective studies, it is difficult to reach a large number of patients in prospective studies. As such, the most important limitation of our study was the smaller number of patients than in previous retrospective studies. One reason for this was that we encountered patients who did not want to share their data. Moreover, the duration of the study could not be prolonged to increase the number of patients; we did not want to encounter any additional problems, such as a change of workplace of the physicians in the clinics.

Conclusion

Based on the results of this study, we assume that both blind and USG-guided biopsies are safe and effective biopsy methods. Regardless of the method used, various degrees of pain may be felt after a biopsy; therefore, the patient should be informed about the probability of pain despite sedation before the biopsy in order to reduce the level of pain. Moreover, liver biopsies performed by experienced physicians or under their supervision may reduce post-biopsy complaints. This research showed that severe pain is not correlated by the biopsy method or patient-specific factors; however, it is related with the biopsy needle used and physician-specific factors. Overall, these results should be supported by future studies with a larger and more diverse patient population.

Ethics

Ethics Committee Approval: The Ethics Committee of Istanbul Medeniyet University, Göztepe Training and Research Hospital approved the present study (01.07.2015-2015/0090).

Informed Consent: Written informed consent received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.K., F.Y.K., G.D., H.C., E.P., A.A., S.T., Y.D., S.E., Z.A., Concept: Z.K., Design: Z.K., F.Y.K., Data Collection and Processing: G.D., H.C., E.P., A.A., S.T., Y.D., S.E., Z.A.,Analysis or Interpretation: Z.K.,Literature Search: Z.K., F.Y.K., Writing: Z.K., F.Y.K.

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Hepatitis C Prevalence and Responses to Pegylated Interferon + Ribavirin Treatment Among Prisoners

Mahkumlarda Hepatit C Prevalansının Saptanması ve Pegile İnterferon + Ribavirin Tedavi Yanıtlarının Değerlendirilmesi

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ABSTRACT

Objective: The aim of our study was to identify the hepatitis C prevalence in prisoners and to share experiences of pegylated interferon (peg-IFN) + ribavirin (RBV) treatment.

Materials and Methods: The study was conducted by assessing the records of prisoners between January 2014 and 2016, retrospectively. Patients in whom planned treatments were applied in a given time were determined and, virologic responses at the end of treatment and 6 months after treatment were evaluated. Chi-square test was used and a p value of less than 0.05 was considered statistically significant.

Results: Among prisoners, the anti-hepatitis C virus (HCV) positivity rate was 7.82% and HCV-RNA positivity rate was 5.72%. The most common genotype was genotype 3a (66 of 99 patients). End-of-treatment and 6th month sustained virologic response rates were 84.6% and 80.5%, respectively. In genotype 3a group, end-of-treatment and 6th month sustained virologic response rates were found to be higher than other genotypes but not statistically significant.

Conclusion: In our study, which assessed prisoners, the rate of HCV positivity was higher than hepatitis C in the general population in Turkey. In accordance with the literature, genotype 3 was the most common genotype among prisoners. Sustained virologic response rates obtained with peg-IFN+RBV treatment suggested that peg-IFN treatment should be used with current treatment combinations in prisoners infected with HCV genotype 3.

Keywords: Hepatitis C, prisoner, prevalence, pegylated interferon + ribavirin

ÖZ

Amaç: Çalışmamızın amacı mahkumlardaki hepatit C prevalansını belirlemek ve pegile interferon (peg-IFN) + ribavirin (RBV) tedavi deneyimlerini paylaşmaktır.

Gereç ve Yöntemler: Çalışma, Ocak 2014 ve 2016 yılları arasında mahkum kayıtlarını retrospektif olarak değerlendirilerek gerçekleştirildi. Belirlenen sürede planlanan tedavilerin uygulanabildiği hastalar tespit edildi, tedavi sonu ve sonraki 6. ay virolojik yanıtları değerlendirildi. Ki-kare testi kullanıldı ve p<0,05 istatistiksel anlamlılık düzeyi olarak kabul edildi.

Bulgular: Mahkumlarda, anti-hepatit C virüsü (HCV) pozitifliği %7,82 ve HCV-RNA pozitifliği %5,72 idi. En yaygın genotip 3a genotipi (99 hastanın 66'sı) idi. Tedavi sonu ve 6. ayda devam eden virolojik yanıt oranları sırasıyla %84,6 ve %80,5 idi. Genotip 3a grubunda, tedavi sonu ve 6. ayda devam eden virolojik yanıt oranları diğer genotiplerden daha yüksek bulundu ancak istatistiksel olarak anlamlı değildi.

Sonuç: Mahkumları değerlendiren çalışmamızda HCV pozitifliği, genel olarak Türkiye'deki pozitifliğe göre daha yüksek bulunmuştur. Literatürle benzer olarak, mahkumlarda genotip 3 en yaygın genotip olarak tespit edilmiştir. Peg-IFN+RBV tedavisi ile elde edilen virolojik yanıt oranları, peg-IFN tedavisinin, HCV genotip 3 ile enfekte mahkumlardaki mevcut tedavi kombinasyonları içerisinde yer alması gerektiğini düşündürmektedir.

Anahtar Kelimeler: Hepatit C, mahkum, prevalans, pegile interferon + ribavirin

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Introduction

Hepatitis C infections are more common among prisoners compared to the general population. The reported prevalence of hepatitis C among prisoners is between 2% and 58% worldwide, with an average of 30% (1,2). Despite the high prevalence, the majority of prisoners are unaware of the presence of hepatitis C infection, and the number of prisoners able to receive appropriate treatment is quite low due to psychological and socio-cultural factors (drug addiction, fear, lack of trust) and prison conditions (difficulties accessing healthcare providers) (3).

Although there have been a few studies investigating the prevalence of hepatitis C among prisoners in Turkey, we did not find any study evaluating treatment response in this group. Therefore, the aim of this study was to determine the prevalence of hepatitis C in prisoners, which is a growing concern in the management of chronic hepatitis C infections worldwide, and to share empirical outcomes of older treatments prior to the use of directly-acting antiviral (DAA) therapy.

Materials and Methods

In this retrospective study, patient records in the infectious diseases outpatient clinics at Gaziantep Dr. Ersin Arslan Training and Research Hospital and Erzurum Training and Research Hospital between January 2014 - 2016 were evaluated. The evaluation included the medical records of all prisoners who presented to the infectious diseases outpatient clinic from the Gaziantep Prison, the Gaziantep E-type Closed Prison Directorate, and the Erzurum Prison Directorate. Patients who tested positive for hepatitis C virus antibody (anti-HCV) were recorded. These patients' sex, age, HCV-RNA values, and HCV genotype were recorded. Viral genotype distributions were compared in terms of geographic variation and age distribution.

The number of HCV-RNA-positive patients who received treatment and the treatment approaches, doses, and duration of the treatment were recorded. It was found that pegylated interferon (peg-IFN) 2a was administered at a fixed dose of 180 mcg and peg-IFN-2b at a dose of 1.5 mcg/kg. Ribavirin (RBV) dosage was 800 mg/day for genotypes 2 and 3, and weight-based for the other genotypes. Treatment initiated for genotypes 1 and 4 was 48 weeks for a patient showing at least 2 log reduction in HCV-RNA in 12 weeks and HCV-RNA negativity at 24 weeks, while a 24-week regimen was administered for genotypes 2 and 3. patients who received treatment for the duration planned (completed treatment) were identified and their end-of-treatment and 6-month post-treatment virologic responses (HVC-RNA results) were recorded.

Statistical Analysis

Sustained virologic response (SVR) rates were compared in terms of viral genotype distributions. The chi-square test was used in comparisons of categorical variables; the Mann-Whitney U test was used in comparisons of non-categorical variables. The statistical significance level was accepted as $p<0.05$.

Results

The records of a total of 1.713 prisoners were reviewed, of whom 134 (7.82%) were positive for anti-HCV. The HCV-RNA positivity rate was 5.72% (n=99). There was viral replication (HCV-RNA positivity) in 73.1% of anti-HCV-positive patients.

Twenty five (1.5%) of the 1.713 prisoners were female and 1.688 (98.5%) were male. Six (4%) of the anti-HCV-positive prisoners were female. The anti-HCV prevalence was 24.0% among females and 7.58% among males.

The mean age of the prisoners was 36.4 (19-72) years. The mean age of the anti-HCV-positive prisoners was 34.8 (19-69) years.

The mean HCV-RNA was 4.034.449 (1.290-17.770.000) IU/mL. Viral genotype in 99 patients was as follows: 3a in 66 (66.7%), 1a in 12 (12.1%), 1b in 19 (19.1%), 2b in 1 (1.0%), and 4 in 1 (1.0%). The prevalence of infection with genotype 3a was higher among inmates in the Gaziantep prisons (55.9% vs. 30%, $p<0.001$). Patients infected with genotype 3a had a lower mean age compared to prisoners infected with other genotypes (37.8 vs. 31.9 years, $p=0.035$).

Seventy nine (79.8%) of the 99 patients were started on peg-IFN (2a or 2b) and RBV (peg-IFN+RBV) therapy. The other 20 patients did not consent to treatment. Treatment was completed in a total of 54 patients and remained incomplete in 25 patients due to non-adherence.

End-of-treatment and 6-month post-treatment SRV rates and genotype distributions of patients who completed treatment are shown in Table 1. Across all genotypes, the SVR rate at 6 months post-treatment was 75.0% (n=33). Seven patients were considered nonresponsive to treatment, recurrence was observed in 4 patients, and 11 patients were not evaluated for SVR at 6 months post-treatment.

Compared to genotype 1, patients with genotype 3 exhibited higher SVR rates at end-of-treatment (83.3% vs. 73.7%, $p=0.441$) and 6 months post-treatment (83.3% vs. 63.2%, $p=0.132$), though the differences were not statistically significant.

Discussion

It is estimated that approximately 130 to 210 million people worldwide are chronically infected with HCV (4). The prevalence of hepatitis C varies geographically, ranging from 0.4% to 0.7% in developed European nations and increasing to 12.5% in Egypt (5,6). The reported prevalence of hepatitis C in Turkey is in the range of 0.4%-2.2% (5,6,7,8,9,10). Various other studies conducted in the Eastern and Southeastern Anatolia regions have determined a hepatitis C prevalence of 1.9% in the Batman area, 2.6% in the Şanlıurfa area, 0.72% in the Diyarbakır area, and 0.8% in the Van area (11,12,13).

The prevalence of hepatitis C also varies when different risk groups are evaluated. Patients with end-stage kidney failure, transplantation patients, males, intravenous (i.v.) drug addicts, and prisoners are shown to have higher rates of hepatitis C infection (5,14,15,16). The results of a meta-analysis by Larney et al. (17)

Table 1. Genotype distributions, end-of-treatment and 6-month post-treatment sustained virologic response rates of treated patients

Genotype distributions n (%)	Number of patients recommended treatment/number of patients who started treatment n=99	Number of patients who started treatment/number of patients who completed treatment n=79	End-of-treatment SVR rates n=54 (%)	Six months post-treatment SVR rates n=44 (%)
Genotype 1a 12 (12.1%)	12/11	11/6	6/6 (100%)	6/5 (83.3%)
Genotype 1b 19 (19.1%)	19/14	14/13	13/8 (61.5%)	13/7 (53.8%)
Genotype 2 1 (1.0%)	1/1	1/0	-	-
Genotype 3 66 (66.6%)	66/52	52/34	34/30 (88.2%)	24/20 (83.3%)
Genotype 4 1 (1.0%)	1/1	1/1	1/1 (100%)	1/1 (%100)
Total	99/79	79/54	54/45 (83.3%)	44/33 (75.0%)

SVR: Sustained virologic response

revealed that the prevalence of anti-HCV among prisoners was 26% worldwide and increased to 64% among prisoners addicted to i.v. drugs. It was reported in the same study that the incidence of HCV, defined as the occurrence of anti-HCV seroconversion, was 1.4% in general, but 16.4% among i.v. drug addicts. According to these data, there are approximately 2.2 million anti-HCV-positive prisoners worldwide, with a large proportion of these in North America and East/Southeast Asia. Zampino et al. (3) showed that the rate of anti-HCV positivity among prisoners varied between 3.0% and 38% depending on factors such as geographic region, i.v. drug use, age, duration of imprisonment, and the prisoners' background.

There are very few studies on this topic conducted in Turkey. Keten et al. (18) determined an anti-HCV prevalence of 17.7% among prisoners in the Kahramanmaraş region. In the present study, we evaluated prisoners in 2 different regions and found anti-HCV positivity at a rate of 7.95% (n=137) and HCV-RNA positivity of 5.86%. These values are higher than previous data regarding the prevalence of hepatitis C in Turkey and in our region.

Although studies indicate that the most common viral genotype in Turkey is currently genotype 1, Altindis et al. (19) demonstrated increases in the rates of genotype 3 (4.78% to 10.06%) and genotype 4 (1.3% to 3.84%) in recent years (in the periods of 2009-2011 and 2012-2014). Studies on prisoners have also determined genotypes 1 and 3 as the most common. Viral genotype distribution may vary based on the geographic area in which the prison is located and the prisoners' background (3,20). In a study conducted by Keten et al. (18) in the Kahramanmaraş region, which has a higher prevalence of genotype 3 than other regions of Turkey, genotype 3 was the most common viral genotype (68.1%) among prisoners (21). We also found that genotype 3 was the most common viral genotype (66.7%) among the prisoners in our study. Studied prisoners from the Gaziantep prison showed higher rates of genotype 3 than studied prisoners from Erzurum, which we attribute to regional variations in genotype distribution. In addition, viral genotype 3 was more prevalent among younger prisoners. These data are consistent with changes in genotype distribution which have been observed recently in Turkey.

Of the 99 patients recommended treatment in our study, SVR was achieved in only 33 at 6 months post-treatment. It appears that inability to persuade patients to undergo treatment, inability to ensure treatment adherence, and noncompliance with post-treatment follow-up are major problems.

Side effects of medications are known to be the leading reason for treatment refusal and discontinuation. It is also known that peg-IFN+RBV therapy can cause side effects which lead to noncompliance with treatment (22,23). Furthermore, numerous factors, such as prison conditions (isolation, frequent prison transfers, etc.), difficulty reaching healthcare providers, and poor diet, increase rates of noncompliance in this patient group, necessitating close follow-up (17). Another reason for treatment interruption is release from prison. It is reported that the average duration of imprisonment is in the range of weeks or months, which makes clinical follow-up difficult, causes interruption of treatment, and prevents post-treatment follow-up (3,16). Therefore, arrangements must be made for prisoners being followed or treated for HCV to continue treatment and follow-up after their release. In addition, it has been noted that the use of curative, completely oral, and short-term (8-12 weeks) DAAs increases prisoners' adherence to treatment (16).

Studies evaluating responses to treatment with peg-IFN+RBV for chronic hepatitis C among prisoners report end-of-treatment SVR rates to be between 28% and 69% (3). SVR rates in prisoners infected with genotype 1 varied between 18% and 43.1%, while those in prisoners infected with genotype 3 were in the range from 50% to 71.4% (3,24,25,26). In the present study, SVR rates at 6 months post-treatment were 75% for all genotypes. We believe that the high SVR rate (83.3%) among genotype 3 patients, which comprise the majority of prisoners undergoing treatment, should be taken into account when developing treatment algorithms.

Of the DAAs used to treat hepatitis C, only sofosbuvir and daclatasvir are shown to be effective against genotype 3 *in vitro* (24). Studies of sofosbuvir+RBV combinations and genotype 3 patients have demonstrated that SVR rates vary based on treatment combination and duration. Feld et al. (27) reported a 60.1% SVR

rate in genotype 3 patients, most of whom were treated with sofosbuvir+RBV combination for 24±2 weeks, with this rate increasing to 84.2% when peg-IFN was added to the treatment combination. Ampuero et al. (22) also demonstrated in their meta-analysis that adding peg-IFN to a 12-week sofosbuvir+RBV treatment combination resulted in a significant increase in SVR rate (75.2% to 92.5%). They stated that the duration of sofosbuvir+RBV treatment must be extended to 24 weeks in order to achieve the same SVR rate that adding peg-IFN provides. Despite effective treatment, the reinfection rate is known to be high, especially among prisoners using i.v. drugs. This emphasizes the importance of a cost-benefit analysis regarding the use of DAAs in prisoners (3). The cost analysis model developed by Martin et al. (28) showed that IFN-free treatments may be cost-effective. Their model included 12-week sofosbuvir+RBV therapy for genotype 3 patients. However, the literature data cited above indicate that this treatment regimen is insufficient to achieve the 95% SVR rate used in the model (22,27).

Study Limitations

The most important limitation for our study is to obtain retrospective data. The other, we observed that the prisoners in our study did not attend follow-up visits in the outpatient clinic, and it was not clear why they discontinued treatment.

Conclusion

Currently, the use of DAAs is recommended for all patient groups, and peg-IFN+RBV therapy is being phased out. However, considering the SVR rates achieved in this and other studies with peg-IFN+RBV, it seems that peg-IFN is still a necessary component in treatment combinations.

Furthermore, simply changing the treatment approach will not eliminate the problems with treatment noncompliance among prisoners in our country, among whom the prevalence of hepatitis C is high. We believe that treatment and follow-up can be made more effective by adopting a holistic perspective which encompasses the periods both during and after incarceration.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: It was not taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Case Report

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Two Rare Causes of Hepatitis: Fascioliasis and Brucellosis

İki Nadir Hepatit Sebebi: Fasioliazis ve Brusellozis

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ABSTRACT

Brucellosis and fascioliasis are zoonoses which induce different type of cell-mediated immune responses and rarely cause hepatitis with together. Brucellosis induces T helper type 1 (Th1) immune response whereas *Fasciola hepatica* induces T helper type 2 (Th2) immune. It may be speculated that chronic fascioliasis can predispose to brucellosis by suppression of Th1 response against brucellosis. In this paper, we present a patient who was diagnosed with brucellosis as well as chronic fasciolasis on the basis of parasite that was seen incidentally during the abdomen ultrasonography. To our knowledge, this case is one of the few cases in the literature that showing the co-infection of the liver by both fascioliasis and brucellosis.
Keywords: Brucellosis, fascioliasis, hepatitis, treatment

ÖZ

Brusellozis ve fasioliazis farklı tiplerde hücresel bağışıklık yanıtını uyaran zoonozlar olup birlikte nadiren hepatit tablosuna neden olurlar. Brusellozis, T yardımcı hücre tip 1 (Th1) ile bağışıklık yanıtını uyarırken *Fasciola hepatica* ise T yardımcı hücre tip 2 (Th2) ile uyarır. Th1 yanıtını baskılaması dolayısıyla kronik fasciola enfeksiyonun brusellozise yatkınlık yarattığı düşünülebilir. Bu yazıda brusellozis tanısına ek olarak batın ultrasonografi ile rastlantısal olarak görülen parazit dolayısıyla kronik fasiolazis tanısı alan bir olgu sunulmaktadır. Literatürde bildiğimiz kadarıyla olgumuz fasiolazis ve brusellozis ile eş zamanlı enfekte olan nadir olgular arasında yer almaktadır.
Anahtar Kelimeler: Bruselloz, fasioliazis, hepatit, tedavi

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Introduction

Fascioliasis is a zoonotic infection caused by *Fasciola hepatica* or *Fasciola gigantica*. Clinical forms of infection include the acute (liver) phase and chronic (biliary) phase. Infection in humans mainly occurs through ingesting uncooked watercress or other fresh aquatic vegetations containing metacercariae, which excystin the duodenum and migrate to the liver parenchyma, where they develop into adult forms (1). On the other hand, brucellosis is a multisystem disease that can mimic many diseases and obscure the diagnosis of other infections (2). Brucellosis and fascioliasis are zoonoses inducing different type of cell-mediated immune responses. Brucellosis and other intracellular bacterial pathogens together with viruses induce T helper type 1 (Th1) immune response via cytokines such as interleukin (IL)-12 and IL-18 whereas helminths like *F. hepatica* induce T helper type 2 (Th2) immune response and increase the levels of immunoglobulin (Ig) E levels eosinophils (3,4).

Case

A 43-year-old female patient was hospitalized at another center three weeks ago because of fever with shaking chills, malaise, nausea, vomiting, epigastric pain, headache, and darkening of the urine color for the past ten days. The patient was discharged from the hospital with doxycycline and rifampin for brucellosis confirmed by the blood cultures positive for *Brucella* spp. After using these medications for only one week, the patient was admitted to our clinic with the same complaints.

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She had a history of raising livestock; ingestion of fresh milk, raw cheese and also watercress near the stream of that region. She had moved from Eastern Anatolia with her family three months ago. Physical examination revealed epigastric tenderness only and all the other vital signs were normal. Laboratory findings were as follows: hemoglobin: 8.9 g/dL, hematocrit: 28.6%, leukocytes: 3900/mm^3, eosinophils: 0.5%, aspartate transaminase: 85 U/L, alanine transaminase: 114 U/L, alkaline phosphatase: 533 U/L, gamma-glutamyl transpeptidase: 423 U/L, total bilirubin: 2.19 (direct bilirubin: 1.71) mg/dL, rose Bengal: (+), and standard wright: 1/160 positive. Due to epigastric tenderness, we performed abdominal ultrasonography which revealed linear mobile structures 15 mm in length considered live parasites within the gallbladder (Figures 1, 2). After this result, in-house serological tests were performed for toxocariasis, fascioliasis, trichinellosis and cystic echinococcosis (CE). Serological findings were as follows: anti-*F. hepatica* ELISA IgG: positive, anti-*Echinococcus granulosus* ELISA IgG: positive (1/640), and *E. granulosus* indirect hemagglutination (IHA): positive (1/640). Parasitological stool tests were performed on three consecutive days and no parasites were detected. Thoracoabdominal computed tomography (CT) was performed for hydatid cyst and there was no radiological sign of echinococcosis. CT revealed a subcapsular hypodense lesion at the level of segment 6 in the liver and 1.2 cm diameter heterogeneity within the gallbladder. Since there was no clinical and radiological finding of hydatid disease, the serologic positivity was thought to be a cross reaction.

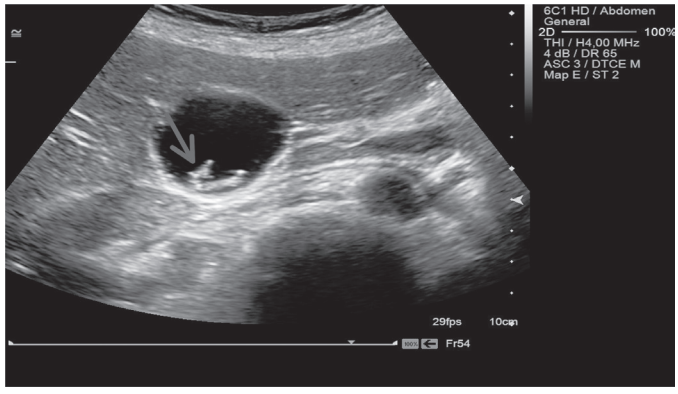

Figure 1. Ultrasonographic image of gall bladder
*Red arrow shows that lineer mobile structures 15.4 mm in length considered as live parasites within the gallbladder

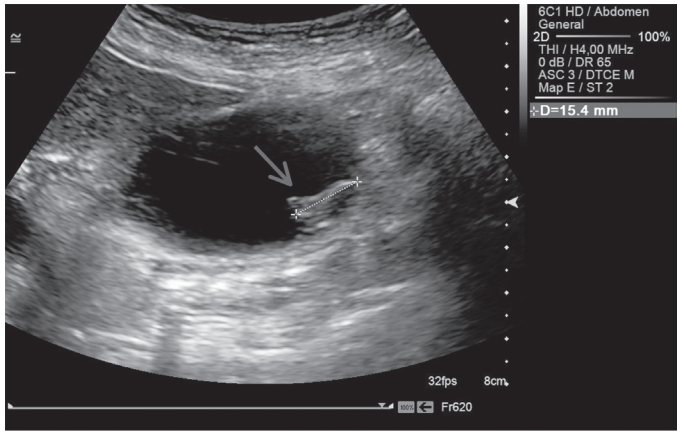

Figure 2. Ultrasonographic image of gall bladder
*Red arrow shows that lineer mobile structures 15.4 mm in length considered as live parasites within the gallbladder in ultrasonography

For the treatment of brucellosis, doxycycline 100 mg q12h (p.o) and rifampin 600 mg q24h (p.o) for six weeks and gentamycin 160 mg q24h (i.m) for two weeks were prescribed. Triclabendazol was also started (10 mg/kg/d; 2 doses, q12h). Screening of three family members was done and one of the family members was found to have fascioliasis (anti-*F. hepatica* ELISA IgG: positive) and treated with triclabendazol as well. Anti-*F. hepatica* ELISA IgG was detected as positive in the patient's control serum eight month after triclabendazol treatment.

Discussion

Brucellosis is an endemic infection in Turkey (2). Brucellosis gives rise to many hepatic manifestations with different patterns. Clinical hepatitis in brucellosis is relatively rare. Buzgan et al. (5) reported that out of 1028 brucellosis patients, elevated liver transaminase levels were seen in 24.8%, whereas hepatic involvement was seen in only 28 (2.7%) patients. Our case also presented as hepatitis with elevated liver transaminase levels.

Brucella antigens induce the pathway of Th1 immune response via cytokines, and Th1 immune response is crucial for recovery from *Brucella* infection. Inadequate response of the Th1 immune system and anergy have been described in patients with chronic brucellosis which is associated with poor outcome (3). Brady et al. (4) described suppression of the *Bordetella pertussis*-specific Th1 response and late bacterial clearance from the lungs in *F. hepatica* coinfected mice. Similar to our case, probably chronic fascioliasis predisposed to brucellosis by the suppression of Th1 response against brucellosis.

F. hepatica has a worldwide distribution, especially in parts of America, China, Europe, Africa, and the Middle East with an estimated 2.4-17 million people infected throughout the world (6). Karahocagil et al. (7) reported a familial outbreak of fascioliasis in Eastern Anatolia similar to our case, all the 24 patients who were diagnosed with fascioliasis had a history of watercress ingestion, lack of appetite, fatigue, malaise and abdominal pain.

The diagnosis of fascioliasis is based on identifying eggs in stool and adult worms in endoscopic or surgical specimens. However, egg detection in faeces with coprological examination is not useful during the acute phase of the disease and has low sensitivity during the chronic phase. In contrast, antibody detection in serum via ELISA method is usually used for the diagnosis of acute infections with high sensitivity and can be used in addition to fecal examination for the latent and chronic infections. Imaging can be an adjunctive tool. Negative stool examinations do not rule out the diagnosis. The eggs are released intermittently from the bile ducts, thus, stool samples may not contain eggs even in infected patients. Therefore it is necessary to perform consecutive analyses of samples (8,9).

Sheep are very good hosts for *F. hepatica* and tend to shed a large number of eggs (up to 20.000 eggs per day). Adult liver fluke produce about 200 times more eggs in sheep than in other species. This makes sheep a very good host for liver fluke (10). Humans are not the primary host for *F. hepatica* and tend to shed a few number of eggs. Among Bolivian children, eggs in stools ranged from 24 to 5064 epg (geometric mean: 201-309 epg) (11).

A prospective study showed a geometric mean level in stools of 233 epg (range: 25-2100 epg) in Porto/Portugal (12). The intensity of egg dischargesis higher in children than in adults (24-4400 epg vs. 144-864 epg) in human endemic area (11). In the presented case, parasitological stool tests were performed on three consecutive days and were found to be negative for fascioliasis. Hence, the diagnosis was made by serological and imaging techniques.

Specific findings on ultrasonography are very helpful in the diagnosis of fascioliasis. Sezgin et al. (12) reported that one of the most common findings was dilatations in the biliary duct with thickening in the duct wall, peripheral hypoechoic nodular lesions, and hyperechoic nonshadowing images filling the common bile duct. Flukes within the gallbladder as in our case and lymphadenopathies were the other important findings.

E. granulosus has a large geographical distribution throughout the world and is a major health problem in many parts of the Mediterranean region, Africa, China and South America. Between the years 2001 and 2005, several hospital and Ministry of Health archives have recorded 14.789 cases of human CE in Turkey (13). The diagnosis of CE is mainly based on radiological and immunological methods. Specificity of the serological tests for CE is limited due to cross-reactions with other helminth diseases, malignancies and liver cirrhosis. When there is no clinical and radiological finding of hydatid disease, serologic positivity for CE is considered as a cross reaction (14). Kaya et al. (15) reported that indirect immunofluorescence assay (IFA) for *E. granulosus* was positive in 59% (13 of 22) of patients with fascioliasis and 8.3% (2 of 24) of healthy people. The titers of antibodies were 1/100 in six and 1/320 in seven patients with fascioliasis. In the presented case, serological findings using in-house assays were: anti-*F. hepatica* ELISA IgG: positive, anti-*E. granulosus* ELISA IgG: positive (1/640), and *E.granulosus* IHA: positive (1/640). Since there was no clinical and radiological finding of hydatid disease, *E. granulosus* positivity was thought to be a cross reaction. In addition, serologic testing for fasciolasis may be useful to rule out this parasitosis in patients from endemic areas (16).

Triclabendazole, a benzimidazole derivative, the only treatment recommended by World Health Organization against fascioliasis, is active against both mature and immature form of parasites, thus, it can be used during the acute and chronic phases. Treatment success is high whereas adverse reactions are usually temporary and mild. The recommended dose of the regimen is 10 mg/kg as a single dose. In clinical practice, if a failure of treatment happens, the dose can be increased to 20 mg/kg in two divided doses 12-24 hours apart (17,18). The presented case was treated with triclabendazol (10 mg/kg/d; 2 doses, q12h).

In relatives of index cases, human fascioliasis can be found in high rates and because of this reason, screening of family members is very important. Eating raw vegetables such as watercress is an important risk factor for families who may acquire the infection in endemic areas. It is recommended that patients presenting abdominal pain and low to high eosinophile levels, who have recently visited an endemic area for *F. hepatica*, should be investigated carefully in order to rule out fascioliasis and, the family members also should be searched (19). In the presented case, screening of three family members was done and one of the family members had fascioliasis detected by serological investigation.

Deveci et al. (20) from Dicle University, Diyarbakir, Turkey have reported a case of fasciola and *Brucella* coinfection in a 39-year-old male patient who was diagnosed via serological and radiological investigations, as in our case.

In the literature, this is one of the rare reported cases from Turkey. To our knowledge, this is one of the few reported cases in the literature that showing the co-infection of the liver by both fascioliasis and brucellosis leading to hepatitis.

Ethics

Informed Consent: It was not taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T., D.D.E, M.K., Concept: H.P., M.T., Design: O.R.S., Data Collection or Processing: U.Ö., Analysis or Interpretation: U.Ö., T.Y., Literature Search: U.Ö., Writing: U.Ö.

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

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Case Report

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A Rare Side Effect of Entecavir: Hepatomegaly and Steatosis

Entekavire Bağlı Nadir Bir Yan Etki: Hepatomegali ve Steatoz

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ABSTRACT

Hepatomegaly and steatosis are rare but potentially fatal side-effects of nucleoside analogues. Here, we present the case of development of hepatomegaly and steatosis in a 53-year-old male who had been treated with entecavir for five years. There were no symptoms of lactic acidosis. At three months after changing entecavir to tenofovir, the liver size returned to normal and maintained within the normal range during the 3-year follow-up. Therefore, it can be presumed that the hepatomegaly and steatosis were due to entecavir therapy. There are very few reports of hepatomegaly and steatosis caused by nucleoside analogues and the majority of the reported cases were associated with lactic acidosis. To the best of our knowledge, there are no previously reported cases of hepatomegaly and steatosis due to entecavir therapy without evidence of lactic acidosis. The aim of this clinical report was to point out a rare side-effect of entecavir and to share our treatment approach.
Keywords: Entecavir, hepatomegaly, steatosis

ÖZ

Hepatomegali ve steatoz nükleozid analoglarının nadir görülen ancak fatal seyredebilen bir yan etkisidir. Bu olgu sunumunda 5 yıl süre ile entekavir tedavisi almakta olan 53 yaşında erkek hastada hepatomegali ve steatoz gelişimi sunulmuştur. Hastada entekavir tedavisi sırasında laktik asidoz bulgusu olmaksızın progresif hepatomegali ve steatoz gelişmiştir. Entekavir tedavisi tenofovir ile değiştirildikten 3 ay sonra karaciğer boyutu normalleşmiş ve tenofovir tedavisinin ilk 3 yılında normal aralıkta seyretmiştir. Bu nedenle, hepatomegali ve steatozun entekavir tedavisine bağlı gelişmiş olması muhtemeldir. Nükleozid analoglarının neden olduğu hepatomegali ve steatoz nadirdir ve bildirilen olguların çoğunda laktik asidoz ile ilişkilidir. Bildiğimiz kadarıyla daha önce entekavir tedavisine sekonder, laktik asidoz bulgusu olmaksızın gelişen hepatomegali ve steatoz olgusu bildirilmemiştir. Bu olgu sunumunun amacı entekavirin nadir görülen bir yan etkisini ortaya koymak ve uygulanan tedavi yaklaşımını paylaşmaktır.
Anahtar Kelimeler: Entekavir, hepatomegali, steatoz

Bal T, Önlen Y, İlkay Şahin S. A Rare Side Effect of Entecavir: Hepatomegaly and Steatosis. Viral Hepat J. 2017;23:80-82.

Introduction

Nucleoside/nucleotide analogues (NAs) are considered the first-line treatment for chronic hepatitis B (CHB) and have been reported to be well tolerated with minor side-effects, even with long-term use (1). Unfortunately, they can also have some rare but serious side-effects. All five NAs carry a black-box warning about the possibility of severe hepatomegaly and steatosis secondary to mitochondrial toxicity in their prescription information on the basis of data from the human immunodeficiency virus (HIV) literature (2,3). However, there have been very few reports of the occurrence of these serious side-effects in CHB patients and all reported cases of hepatomegaly and steatosis have been associated with lactic acidosis and most of the patients had impaired liver function (4,5,6). The case is here reported of a non-cirrhotic CHB patient who developed hepatomegaly and steatosis associated with long-term administration of entecavir monotherapy.

Case

We report a 53-year-old male non-cirrhotic patient with CHB who has been treated with entecavir since November 2008. A preliminary ultrasound of the abdomen revealed a normal liver size. After 5 years of treatment (in January 2014), ultrasonography showed 163 mm hepatomegaly and steatosis. Six months later, the liver size had increased progressively and on the last ultrasonography,

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the liver size of the patient was 175 mm in diameter. He had no symptoms of lactic acidosis such as abdominal pain, shortness of breath, muscle pain or weakness. Physical examination revealed a palpable liver edge 2 cm below the right costal margin. The patient was mildly overweight with a body mass index (BMI) of 28. The serum aminotransferase, bilirubin, creatinine, thyroid function and blood lipids levels were all within the normal ranges. Moderate fibrosis (stage: 2) and moderate necro-inflammatory activity (histological activity index: 9) were determined on the liver biopsy which had been performed before the initiation of entecavir therapy. There was no history of exposure to any other NAs, alcohol abuse, congestive heart failure or metabolic syndrome. When this side effect was identified, entecavir was changed to tenofovir. After receiving tenofovir therapy for 3 months, abdominal ultrasound showed a normal liver size. Moreover, the size of the liver has been maintained within the normal range throughout 3 years of tenofovir therapy. In addition, there was no significant change in alanine aminotransferase, aspartate aminotransferase or HBV DNA levels, thyroid function tests, lipid profile and BMI during this period (Table 1).

Table 1. Comparison of the variables between time points (before initiation of tenofovir therapy, at 3-month and 3-year of tenofovir therapy)

Variable	Baseline	3 Months	3 Years
BMI, kg/m^2	28	28	28
ALT level, U/L	17	20	25
AST level, U/L	19	22	23
Total cholesterol, mmol/L	197	182	198
LDL cholesterol, mmol/L	115.9	126	117.5
Triglyceride, mmol/L	188	145	123
HBV DNA level, IU/mL	<20	<20	<20
TSH, IU/mL	2.25	2.23	2.06
Free T4, pg/mL	1.04	1	1.09
Free T3, pg/mL	2.85	2.48	2.89

BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HBV: Hepatitis B virus, TSH: Thyroid stimulating hormone, T4: Thyroxine, T3: Triiodothyoxine, LDL: Low-density lipoprotein

Discussion

The case here described progressive hepatomegaly and steatosis without evidence of lactic acidosis in a patient undergoing entecavir monotherapy for CHB infection. There was no evidence to support other etiologies of hepatomegaly and steatosis such as alcohol abuse, congestive heart failure, obesity, metabolic syndrome or hypercholesterolaemia. Moreover, after cessation of entecavir, the liver size returned to normal within 3 months. It can therefore be considered that the hepatic steatosis and hepatomegaly were most likely caused by the entecavir therapy.

There are currently five NAs approved in Turkey for the treatment of CHB; including lamivudine, adefovir dipivoxil, telbivudine, entecavir and tenofovir dipivoxil fumarate. NAs block hepatitis B virus (HBV) replication by inhibiting the HBV polymerase enzyme. As they can also inhibit human mitochondrial DNA polymerase gamma (which has a structure similar to that of HBV polymerase enzyme), in some cases, they can cause severe mitochondrial toxicity (7). However, there are insufficient data about which risk factors are predisposing to mitochondrial toxicity of NAs. Previous studies have suggested that the presence of cirrhosis and taking a combination therapy with NAs is associated with an increased risk of mitochondrial toxicity (4,5). In contrast, the current case was non-cirrhotic and was taking entecavir monotherapy.

The clinical presentation of mitochondrial toxicity is variable and depends on the target organ that is involved. On the basis of data from previously published studies of HIV-infected patients, NAs-related mitochondrial toxicity may present with lactic acidosis, neuropathy, myopathy, pancreatitis and hepatotoxicity, including severe hepatomegaly and steatosis (7,8). Nevertheless, there have been only a few reports of patients with CHB infection who have developed at least one of these mitochondrial toxicity forms due to NAs medication. In addition, most of them were taking these drugs as part of combination antiretroviral therapy (ART) for HIV/HBV co-infection (4,5,9). Thus, the question of whether there is any link between the use of NAs and mitochondrial toxicity in HBV-infected patients remains controversial.

The development of NAs-related hepatomegaly and steatosis without the occurrence of lactic acidosis has been reported in HIV-infected patients (10). However, there have been no previously published cases of HBV-infected patients with isolated hepatomegaly and steatosis attributed to the use of NAs. Although, the blood level of the current case was unknown, there were no signs or symptoms of lactic acidosis/hyperlactatemia on presentation. Therefore, decompensated, lactic acidosis was discounted. Even though, the clinical significance of this is unknown, subclinical elevations in lactate level have been described in HIV-infected patients receiving NAs therapy (11). Therefore, the possibility of chronic, compensated, asymptomatic hyperlactatemia cannot be ruled out in the current case.

In prescription information of all five NAs approved for CHB, discontinuation of NAs is recommended in patients who develop this severe side-effect (2,3). This may be because it is not known whether this mild syndrome can change from a mild to a severe form.

According to a literature review of HIV-infected patients with symptoms of mitochondrial toxicity, discontinuation of ART and changing the class of ART regimens after completely resolution of symptoms is recommended (12). Symptoms of mitochondrial toxicity will generally resolve once treatment stopped, although it can also be fatal even after discontinuation of NA (2). However, there are insufficient data to make recommendations about HBV-infected patients. As there were no signs or symptoms of lactic acidosis/hyperlactatemia in the current case, anti-HBV therapy was not terminated. As no treatment option other than NAs is available for the underlying HBV infection and the European Association for the Study of the Liver guidelines recommend the long-term administration of a potent NA for treatment of CHB infection, entecavir was changed to tenofovir, which is another potent alternative agent (13). During a 3-year follow-up, the patient did not show any relapse and the size of the liver has been maintained within the normal range without steatosis. This case highlights

the importance of considering hepatomegaly and steatosis as side-effects of entecavir therapy. For patients developing these potentially fatal side-effects of entecavir, changing the therapy to tenofovir would appear to be safe. Nevertheless, further long-term experience is required.

Ethics

Informed Consent: Informed consent form was taken from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.B., Y.Ö., S.I.Ş., Design: T.B., Y.Ö., S.I.Ş., Data Collection or Processing: T.B., Y.Ö., S.I.Ş., Analysis or Interpretation: T.B., Y.Ö., S.I.Ş., Literature Search: T.B., Writing: T.B., Y.Ö., S.I.Ş.

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

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In the Light of European Association for the Study of the Liver 2017: Terminology and Approach to Hepatitis B Virus Reactivation in Patients at High Risk

Avrupa Karaciğer Araştırmaları Derneği 2017 Işığında: Yüksek Riskli Hastalarda Hepatit B Virüsü Reaktivasyonuna Yaklaşım ve Terminoloji

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Keywords: Hepatitis B virus reactivation, terminology, prevention
Anahtar Kelimeler: Hepatit B virüsü reaktivasyonu, terminoloji, önleme

Kayaaslan B, Güner R. In the Light of European Association for the Study of the Liver 2017: Terminology and Approach to Hepatitis B Virus Reactivation in Patients at High Risk. Viral Hepat J. 2017;23:83-85.

Dear Editor,

Reactivation of hepatitis B virus (HBV) is a prevalent and important problem in transplant recipients receiving immunosuppressive treatment for prevention of organ rejection or in those who receive chemotherapy for lymphoma or leukemia (1). It is defined as a sudden increase in HBV replication in patients with inactive or resolved hepatitis B, in hepatitis B surface antigen (HBsAg) carriers and HBsAg-negative but anti-hepatitis B core (HBc)-positive patients (2). The current guidelines recommend HBV screening in patients who will receive cancer chemotherapy or immunosuppressive therapy and in those who are candidate for organ transplantation. All patients with active or inactive disease or resolved HBV infection are at risk for HBV reactivation in different degree depending on the type of immunosuppressive therapy. Treatment recommendations are based on the patients' risk group (1,3,4). Reddy et al. (4) have described the recommendation of the American Gastroenterological Association Institute systematically about prevention and treatment of HBV reactivation during immunosuppressive drug therapy in detail.

HBsAg, anti-HBs and anti-HBc total antibody should be screened prior to initiation of immunosuppressive treatment (5,6,7). There are some differences in the management of prevention of hepatitis B reactivation in the literature. We assume that these differences result from the confusion in nomenclature. In this report, we aimed to draw attention to the fact that there is a need for using standardized nomenclature and definition about recommended therapy for risky population.

In the literature, terms such as "prophylactic", "pre-emptive" and "therapeutic" antiviral therapy are used to describe recommended treatment option for prevention of HBV reactivation in patients infected with HBV who undergo immunosuppressive treatment. There is no enough description about the use of "prophylactic, pre-emptive and therapeutic antiviral therapy" terms in the current clinical guidelines for hepatitis B, although they contain recommendations for prevention of reactivation in this patient populations (5,6,7). The distinction between "prophylactic" and "pre-emptive" treatment has not been clearly understood in the European Association for the Study of the Liver (EASL) 2012

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clinical practice guideline. "Pre-emptive treatment" has been recommended for HBsAg-positive patients during treatment and 12 months after discontinuation of therapy regardless of HBV DNA levels (8). The last updated EASL 2017 guideline does not use the term "pre-emptive treatment" in this patient population and recommends the use of nucleos(t)ide analogues (NAs) for prophylaxis and treatment. The guideline recommends pre-emptive treatment in HBsAg-negative, anti-HBc-positive patients with moderate or low-risk of HBV reactivation and describes the meaning of pre-emptive treatment. Initiation of prophylactic NAs in HBsAg-negative and anti-HBc-positive patients at high-risk for HBV reactivation has been remarked as recommendation of some experts in EASL 2012 guideline. EASL 2017 offers anti-HBV prophylaxis in these patient populations as guideline recommendation (6).

The Asian Pacific Association for the Study of the Liver (APASL) guideline on the management of hepatitis B infection recommends "prophylactic" antiviral therapy in HBsAg-positive cancer patients and in those who undergo solid organ transplantation or receive immunosuppressive agents for auto-immune and rheumatic diseases. The guideline recommends prospective follow-up of alanine aminotranspherase (ALT) and HBV DNA testing in HBsAg-negative and anti-HBc-positive patients with undetectable serum HBV DNA who receive chemotherapy and/or immunosuppression, regardless of anti-HBs status and treatment with NA therapy upon confirmation of HBV reactivation before ALT elevation (7). This strategy was named as "pre-emptive" antiviral treatment in a literature review by Hwang and Lok (1) in which the most descriptive definition of recommended therapy for prevention of HBV reactivation have been made. They have proposed use of the term "preventive antiviral therapy" as antiviral therapy started when ALT and/or HBV DNA levels increase and there are no signs of jaundice or liver failure when antiviral therapy is initiated in patients receiving immunosuppressive therapy. The guideline of the American Society of Transplantation (AST) for viral hepatitis in solid organ transplantation does not recommend routine antiviral prophylaxis in patients with resolved hepatitis B infection (HBsAg-negative, anti-HBc-positive ± anti-HBs-positive) who undergo immunosuppressive treatment. However, the AST recommends initiating "prophylactic antiviral treatment" in patients with increased risk for HBV reactivation (anti-HBc-positive alone or intense immunosuppression) or alternately monitoring HBV DNA and HBsAg level and initiating "pre-emptive antiviral treatment" if HBsAg becomes positive or if HBV DNA progressively rises (9). The meaning of the terms of "prophylactic" and "pre-emptive" antiviral treatment in the AST guideline are similar to those defined by Hwang and Lok (1). We think that it is better the current guidelines use this nomenclature and explain the meaning of the terms when they recommend an approach for the prevention of HBV reactivation.

A similar confusion is also available in a review about antiviral treatment in renal transplant patients written by Ridruejo (10). In the review, "antiviral treatment" has been recommended in patients with chronic hepatitis B and "prophylactic", "pre-emptive" or "salvage therapy" in inactive hepatitis B carriers based on HBV DNA level and hepatocellular histology. The meaning of the terms is poorly understood. The other topic we want to point out is the contradictions in treatment recommendations in the review. Pre-emptive therapy is recommended in patients with HBV DNA ≤2000 IU/mL, while prophylactic antiviral therapy is recommended in HBV DNA-negative patients. We think that the recommendation on pre-emptive therapy is an imprudent approach especially in HBV DNA-positive organ transplant patients. The reviewer also recommends starting treatment at least 2 weeks before renal transplantation in those with HBV DNA ≤2000 IU/mL in the section of timing of initiation of treatment. This suggestion is not compatible with the definition of prophylactic and pre-emptive treatment.

The EASL 2017 guideline has corrected the terminology confusion in the previous version. The recommendations of the updated EASL 2017, AST guideline and the APASL guideline are parallels to approach to HBV reactivation in high-risk patients (6,7,9). In the light of the EASL 2017 guideline, prophylactic/pre-emptive (on-demand) and therapeutic approaches are standardized according to the patients' hepatitis B status and the type of immunosuppressive treatment (6). We think that this algorithm becomes a reasonable and non-confusing approach to HBV reactivation.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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