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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" (2013, 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: www.viralhepatitdergisi.org. Past issues of the journal are also available at this website. Manuscripts should submitted online from www.journalagent.com/vhd

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 2013) (http://www.wma.net/en/30publications/10policies/b3/). 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). In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights as per the Guide for the Care and Use of Laboratory Animals (http://oacu.od.nih.gov/regs/guide/guide.pdf) and they should obtain animal ethics committee approval.

The content of the submitted manuscripts should conform to the criteria stated in Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication published by International Committee of Medical Journal Editors and updated in October 2008 (available at http://www.icmje.org/).

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 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.

The journal does not charge from the author for published articles and there is no royalty payment to the authors.

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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 (2013, 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 Engilish)

ii. Turkish and english Abstract (max 300 words)

iii. Turkish and english Key Words

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.

• Author number for review articles should not exceed three.

• 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.

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

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

ARTICLE SECTIONS

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

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.

Figures, Pictures, Table 's and Graphics:

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

• Figures, pictures/photographs must be added to the system as separate .jpg or .gif files.

• The manuscripts containing color figures/pictures/tables would be published, if accepted by the Journal. In case of publishing colorful artwork, the authors will be asked to pay extra printing costs.

• All abbrevations used, must be listed in explanation which will be placed at the bottom of each figure, picture, table and graphic.

• For figures, pictures, tables and graphics to be reproduced relevant permissions need to be provided. This permission must be mentioned in the explanation.

• Pictures/photographs must be in color, clear and with appropriate contrast to separate details.

Conflict of interest: If any of the writers have a relationship based on self-interest, this should be explained.

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 '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

• Complete and accurate references and citations

• List of references styled according to "journal requirements"

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EDITORIAL

Dear Colleagues,

We are here again with a new issue and some news. We will be happy to give you a good news. Viral Hepatitis Journal began to indexed in Emerging Sources Citation Index (SCI-E). Your articles that published in our journal along with this number will be indexed in Emerging Sources Citation Index (ESCI).

In this ıssue, there are one review article about "Chronic Viral Hepatitis in Human Immunodeficiency Virus-infected Patients" and four articles about "Telaprevir-based Triple Therapy for Retreatment of Chronic Hepatitis C Patients with Genotype Four Followed in Our Clinic", "Can Detection of Non-alcoholic Fatty Liver Disease be Coincidental in Young Patients with Chronic Hepatitis B?" "The Frequency of Hepatitis B Virus, Hepatitis C Virus and Human Immunodeficiency Virus Infections among Patients with Schizophrenia in a Mental Health Hospital in Turkey", "Red Cell Volume Distribution Width to Platelet Ratio is an Important Predictor of Liver Fibrosis and Cirrhosis in Chronic Hepatitis B".

Also; "Seroprevalence Rates of Hepatitis B Surface Antigen, Anti-Hepatitis C Virus and Anti-Human Immunodeficiency Virus ½ Certain Risk Groups", "Seroprevalence of Hepatitis B Virus, Hepatitis C Virus and Human Immunodeficiency Virus among Healthcare Staff in a State Hospital" and "Liver Biopsy is the Gold Standard at Present, How about Tomorrow?", subjects were included in the Letter to editor in this issue.

We expect your contributions with articles, case reports, reviews, and letters to editor.

Best wishes

Prof. Dr. Fehmi TABAK **Prof. Dr. Mustafa ALTINDİŞ**

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Viral Hepat J 2016;22(2):39-42

Chronic Viral Hepatitis in Human Immunodeficiency Virus-infected Patients

İnsan Bağışıklık Yetmezlik Virüsü Enfeksiyonu Olan Hastada Kronik Viral Hepatit

Uluhan SİLİ, Aysun TEKİN, Volkan KORTEN

Marmara University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

ABSTRACT

Infectious diseases physicians taking care of human immunodeficiency virus-infected patients should investigate for the presence of chronic hepatitis caused by hepatitis B and hepatitis C virus infections. This is important as chronic viral hepatitis progresses more rapidly to end-stage liver disease in human immunodeficiency virus-infected patients. Once diagnosed, there are effective drugs for the treatment chronic viral hepatitis. Tenofovir containing anti-retroviral therapy effectively suppresses hepatitis B replication. Hepatitis C cure can be achieved with directly acting antiviral agents.
Keywords: Human immunodeficiency virus, chronic hepatitis B, chronic hepatitis C, co-infection

ÖZ

İnsan bağışıklık yetmezlik virüsü ile enfekte hastalarda kronik hepatit B virüsü (HBV) ve hepatit C virüsü (HCV) enfeksiyonları da araştırılmalıdır. Bu hastalarda kronik viral hepatitler daha hızlı ilerler ve siroz daha çabuk gelişir. Tanı konulduktan sonra kronik viral hepatitler için etkin tedavi verilebilir. HBV'nin replikasyonunu tenofovir içeren anti-retroviral tedaviler ile baskılamak mümkündür. Doğrudan etkili antiviral ilaçların geliştirilmesiyle HCV enfeksiyonunun sağaltımı mümkün hale gelmiştir.
Anahtar Kelimeler: İnsan bağışıklık yetmezlik virüsü, kronik hepatit B, kronik hepatit C, ko-enfeksiyon

Sili U, Tekin A, Korten V. Chronic Viral Hepatitis in Human Immunodeficiency Virus-infected Patients. Viral Hepat J 2016;22:39-42

Introduction

As hepatitis B virus (HBV) and hepatitis C virus (HCV) are transmitted through contact with infectious blood and body fluids, they should be investigated in patients with human immunodeficiency virus (HIV) infection (1). Diagnosing chronic viral hepatitis in HIV-infected patients is important as progression to end-stage liver disease is more rapid in this patient population. HBV replication can be suppressed with nucleosid(t)e reverse transcriptase inhibitors (NRTIs) within antiretroviral therapy (ART) combinations that inhibit HBV polymerase along with HIV-reverse transcriptase. HCV cure has recently become possible using direct-acting antiviral (DAA) agents, although there are accessibility issues to these drugs in resource-limited settings.

General recommendations for chronic viral hepatitis patients are also applicable for HIV co-infected patients (2). These patients should be vaccinated for hepatitis A virus (HAV) if determined to be seronegative. Alcohol consumption should be decreased to minimum or ceased, if possible. Lifelong surveillance for hepatocellular carcinoma is recommended for patients with fibrosis even after chronic viral hepatitis is controlled or cured (3).

Epidemiology

Globally, 5-10% of patients with HIV are HBsAg (+) (4). Two Turkish HIV cohorts reported hepatitis B surface antigen (HBsAg) prevalence as 6.2% [59 of 949 patients, ACTHIV-IST cohort, (5)] and 5.7% (33/574, HIV-TR cohort; Korten V, personal communication). HBsAg seroprevalence is reported to be 2.5-9% in the general Turkish population (6).

In developed countries, anti-HCV positivity can be up to 25% in HIV-infected patients (7,8). ACTHIV-IST and HIV-TR cohorts reported 0.9% (9 of 949 patients) and 3.3% (18 of 534 patients) anti-HCV positivity, respectively [(5); Korten V, personal communication). The prevalence of anti-HCV positivity has been reported to be 1-2.2% in the general Turkish population (6).

The above mentioned cohort studies suggest similar seroprevalence rates for chronic viral hepatitis between the general population and HIV-infected patients in Turkey. In countries where

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higher seroprevalence rates for chronic viral hepatitis among HIV-infected patients are reported, this situation is usually attributed to higher intravenous drug user rates among HIV-infected patients (7). In Turkey, HIV is mainly sexually transmitted and intravenous drug use rates are lower in general as well as in HIV-infected Turkish patients (9,10).

Hepatitis B Virus Infection in Human Immunodeficiency Virus-infected Patients

Serological status of the patient should be determined by analysis of HBsAg, anti-HBc-immunoglobulin G (IgG) and anti-HBs, and HBV-unexposed patients should be immunized. HBsAg (+) patients should be evaluated for chronic liver disease by means of biochemical tests (e.g., albumin, the international normalized ratio) and radiological methods (e.g., liver ultrasonography and/or magnetic resonance imaging) (1). If cirrhosis is suspected, a liver biopsy should be performed. In recent years, non-invasive methods to assess liver fibrosis, such as transient elastography, AST to platelet ratio index, and fibrosis-4 score, have been gaining popularity.

It is important to determine anti-HBc-IgG not to miss HBsAg (-) and anti-HBs (-) occult chronic HBV infection (1). HBV-DNA analysis should be performed in patients with isolated anti-HBc-IgG positivity to rule out chronic hepatitis, especially in those with elevated hepatic transaminases.

HBsAg (+) patients should be evaluated for the chronic HBV infection phase they are in (i.e., immune-tolerant, HBeAg-positive chronic hepatitis, inactive chronic hepatitis B, or HBeAg-negative chronic hepatitis B) and be treated accordingly (11).

Progression of acute HBV infection to chronicity is more common in HIV-infected patients (12). Moreover, HBV/HIV co-infected patients have higher HBV-DNA levels leading to faster fibrosis development (12). Liver-related mortality rate is 17.75 times higher in co-infected patients than in HBV mono-infected patients (13). On the other hand, HBV co-infection does not affect HIV/ acquired immunodeficieny syndrome (AIDS) progression (14).

Treatment of Chronic Hepatitis B Virus in Human Immunodeficiency Virus-infected Patients

ART is indicated in patients with HIV/HBV co-infection independent of CD4 value (2). The goal is to prevent disease progression due to HBV as well as HIV. The recommended NRTI backbone for HIV treatment involving tenofovir and emtricitabine has dual anti-HBV activity. This is the recommended backbone for ART in co-infected patients (2). If a switch is required to abacavir/lamivudine or zidovudin/lamivudine, anti-HBV activity of lamivudine has to be supported with entecavir if tenofovir cannot be used. This is important as not only high rates of resistance develop with lamivudine mono-therapy, but also a valuable high genetic barrier drug, entecavir, can be lost due to cross-resistance. If a switch to NRTI-free treatment is chosen, suppression of HBV has to be maintained with entecavir or tenofovir as patients with advanced fibrosis can easily be decompensated. Tenofovir alefenamide, which is not yet available in Turkey, is poised to replace tenofovir disoproxil fumarate in the near future. This equally effective but less toxic derivative of tenofovir is probably effective against HBV although studies are lacking at this point (15).

The goal is to achieve a complete virological response, which is defined as undetectable HBV-DNA with a sensitive polymerase chain reaction (PCR) test at 24 to 48 weeks of anti-viral therapy (16). In addition to a complete virologic response, HBsAg loss is also a desirable outcome; however, this serologic response is rare (16).

Hepatitis C Virus Infection in Human Immunodeficiency Virus-infected Patients

Anti-HCV serological status should be checked in HIV-infected patients (1). In anti-HCV (+) patients, HCV-RNA should be quantified and, if viremia is present, HCV genotype should be determined. In HIV-infected patients with alanine transaminase/aspartate transaminase (ALT/AST) elevations, HCV infection should be ruled out. In patients with unexplained ALT/AST elevations and negative anti-HCV, HCV-RNA should be checked for the possibility of false sero-negativity or recent infection. Patients with HCV viremia should be evaluated for chronic liver disease with methods described above for HBV.

HCV infection progresses more rapidly to cirrhosis with a relative risk of 2.92 in HIV-infected patients (17). On the contrary, HCV infection does not seem to affect HIV disease progression (18).

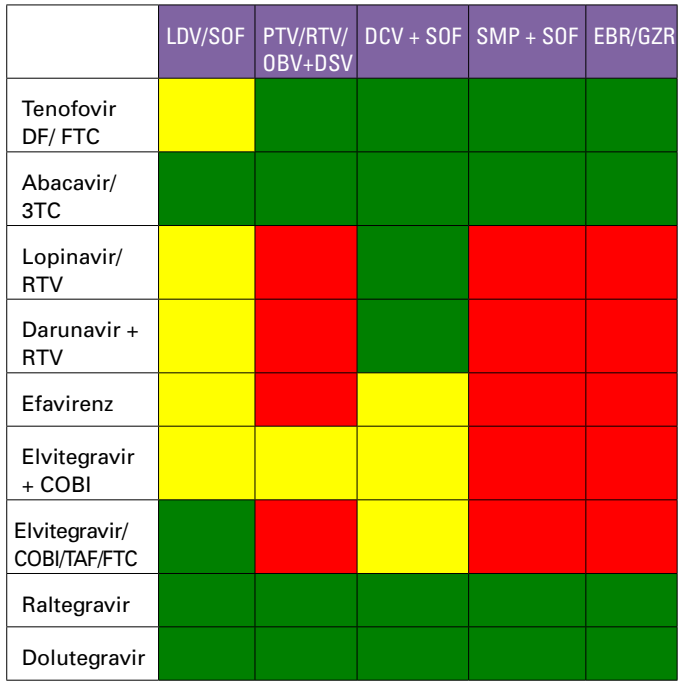

Figure 1. Selected antiretroviral therapy drugs/combinations and their interactions with most current direct-acting antiviral agents (red, co-administration not recommended; yellow, potential interaction that may require monitoring or dose adjustment; green, no significant interaction was observed or expected) [adapted from ref. (15,21)] For most current information, check human immunodeficiency virus drug Interactions website maintained by University of Liverpool- http://www.hiv-druginteractions.org-)
3TC: Lamivudine, COBI: Cobicistat, DCV: Daclatasvir, DF: Disoproxil fumarate, DSV: Dasabuvir, EBR: Elbasvir, EVG: Elvitegravir, FTC: Emtricitabine: GZR: Grazoprevir, LDV: Ledipasvir, OBV: Ombitasvir, PTV: Paritaprevir, RTV: Ritonavir, SMV: Simeprevir, SOF: Sofosbuvir, TAF: Tenofovir alefenamide

Table 1. Points to consider before switching antiretroviral therapy in patients with suppressed human immunodeficiency virus*
Review ART history (previous intolerance to ART combinations, virological failure)
Review results of previous resistance tests
Switch to a new regimen only if virological suppression will be possible
Caution while switching from protease inhibitor containing ART regimens when drug resistance is suspected
Consult with experts on HIV drug resistance if unsure of which ART combination to choose
Check HIV viral load every month for the first three months after the switch
Maintain anti-HBV activity in HBV co-infected after the switch
ART: Antiretroviral therapy, HIV: Human immunodeficiency virus, HBV: Hepatitis B virus *adapted from ref (2).

Treatment of Chronic Hepatitis C Virus in Human Immunodeficiency Virus-infected Patients

HCV co-infection is an indication for ART independent of CD4 levels (2). ART decreases hepatic decompensation risk due to HCV by 28-41% (19). However, it is still higher than in HCV mono-infected patients (20). For this reason, HCV should also be treated in HIV-infected patients receiving ART. The goal of HCV therapy is to achieve a sustained virological response (SVR), defined as undetectable HCV-RNA with a sensitive PCR test at least 12 weeks after completion of therapy (21).

HCV is now a curable disease with the development of DAA agents (22). For a long time, pegylated interferon-alpha and ribavirin were used in patients with HIV with suboptimal response rates (23). Not only this therapy was hard to tolerate due to side effects, but also SVR rates were 15-25% lower than that in HCV mono-infected patients (24). These agents are no longer recommended for HCV treatment (2). DAAs can cure HCV in HIV-infected patients with response rates similar to that in HCV mono-infected patients (92-100% SVR rates) (15,24). However, emerging real-world data suggest lower SVR rates than those reported in clinical trials (25,26). For the most common genotype in Turkey, GT1b, 12 weeks of DAA without ribavirin is recommended for non-cirrhotic patients (21). Unlike mono-infected patients, shorter eight-week treatment is not recommended for HIV/HCV co-infected patients. As HCV treatment field is rapidly evolving, current information should be checked from up-to-date websites, such as http://hcvguidelines.org. Treatment rules imposed by social security institution of Turkey should be observed for state-insured patients (27).

One question is timing of DAA in patients receiving ART. If DAA is going to be administered with ART, drug-drug interactions and overlapping toxicities should be considered (Figure 1). The most likely three clinical scenarios are presented below:

Scenario 1: Chronic HCV is diagnosed concomitantly with HIV. If there is no urgent need to start ART (i.e., CD4 >500 cells/mm^3, no opportunistic infections, no AIDS-defining illness), DAA could be started before ART with the goal of curing HCV and avoiding any drug-drug interactions. In this case, chosen DAA should not have any anti-HIV activity for example; paritaprevir, ritonavir, ombitasvir, dasabuvir (PrOD) regimen contains ritonavir, which has anti-HIV activity and may select for protease inhibitor resistance if given alone. In cases where ART has to be started immediately (i.e., CD4 <200 cells/mm^3 or an AIDS-defining illness is present), the current recommendation is to delay HCV treatment. In these patients the goal is to start ART, achieve virological suppression, and start immune reconstitution first.

Integrase inhibitors (without the pharmacologic booster) with NRTI backbone are the least likely ART combinations to interact with DAAs (Figure 1). In terms of DAA, daclatasvir/sofosbuvir regimen is the most compatible with different ART combinations. As ledipasvir increases tenofovir levels, monitoring for tenofovir-associated renal toxicity is recommended if tenofovir and ledipasvir are co-administered (21).

Scenario 2: HIV/HCV co-infected patients stable on ART and now eligible for HCV treatment with newly available DAAs. ART cessation is not recommended to start DAA. However, drug-drug interactions and overlapping toxicities may dictate ART switch. The foremost principle of regimen switch is to maintain viral suppression without compromising future treatment options (2). Points to consider before ART switch are summarized in Table 1.

Scenario 3: HIV patient on ART developing acute HCV. The most recent European AIDS Clinical Society guideline recommends treatment of acute HCV with pegylated interferon and ribavirin if spontaneous resolution does not happen within one to three months, as response to treatment declines with prolonged wait (1). However, as new DAAs are effective in curing chronic HCV with almost 100% success rate, one can easily wait for up to one year and treat if spontaneous resolution does not take place within that time frame (21). Current treatment rules imposed by social security institution of Turkey allows six months of treatment with pegylated interferon-alpha for patients with acute HCV infection (27).

Conclusions

Chronic HBV and HCV have to be diagnosed and treated, as liver disease progresses more rapidly in HIV-infected patients. For HIV/HBV-infected patients, tenofovir/emtricitabine backbone is ideal. During ART switches, suppression of HBV replication has to be maintained to avoid flare or decompensation risk. HCV can be cured using DAAs in HIV-infected patients at rates similar to those in HCV mono-infected patients. The main issue other than availability and cost of these drugs is to watch for drug-drug interactions and overlapping toxicities between DAAs and ART. Integrase inhibitors as a part of ART seem to have the least potential to interact with other drugs. Further liver injury should be prevented by vaccination or abstinence and hepatocellular carcinoma surveillance should be employed for patients at risk.

Ethics

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Uluhan Sili, Concept: Uluhan Sili, Design: Uluhan Sili, Data Collection or Processing: Uluhan Sili, Aysun Tekin, Analysis or Interpretation: Uluhan Sili, Volkan Korten, Literature Search: Uluhan Sili, Aysun Tekin, Writing: Uluhan Sili.

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Can Detection of Non-alcoholic Fatty Liver Disease be Coincidental in Young Patients with Chronic Hepatitis B?

Genç Kronik Hepatit B Hastalarında Alkolik Olmayan Yağlı Karaciğer Hastalığı Saptanması Rastlantısal Olabilir mi?

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ABSTRACT

Objective: The objective of this study was to determine the factors associated with the presence of non-alcoholic fatty liver disease (NAFLD) in young persons who are hepatitis B surface antigene (HBsAg)-positive and negative, and to investigate if NAFLD coexisting hepatitis B virus (HBV) is coincidental.

Materials and Methods: This retrospective study, conducted in a military hospital in Turkey, included a total of 384 subjects. The subjects were divided into two groups according to the presence of NAFLD detected by ultrasonography (US). Sociodemographic characteristics, biochemical, histopathological, virological and US results were recorded . Statistical analysis was performed using SPSS 22.0.

Results: The median age of the patients, all of whom were male, was 26 years (20-40). NAFLD was identified in 16.9% of patients. HBsAg positivity was found in 36.9% of patients with NAFLD. It was remarkable that no statistically significant difference was found in HBsAg positivity between the patients with and without NAFLD (p=0.661). NAFLD was found in 13.2% of HBsAg-positive patients. NAFLD was determined in 20.3% of HBsAg-negative patients. No significant difference was found in NAFLD grades between HBsAg-positive and negative patients (p=0.158). In the present study, only γ-glutamyl transferase in HBsAg positive patients, and age, alanine transaminase and aspartate transaminase in HBsAg negative patients were determined as the most important factors associated with the presence of NAFLD.

Conclusion: We found that HBsAg positivity is not correlated with the development of NAFLD in young patients, and coexistence of NAFLD and HBV might be coincidental.

Keywords: Non-alcoholic fatty liver disease, chronic hepatitis B, ultrasonograpy

ÖZ

Amaç: Bu araştırmanın amacı hepatit B yüzey antijeni (HBsAg) pozitif ve negatif genç hastalarda alkolik olmayan yağlı karaciğer hastalığının (AOYKH) sıklığını, AOYKH oluşumu ile ilişkili faktörleri ve hepatit B virüsü (HBV) ile AOYKH'nin birlikte saptanmasının rastlantısal olup olmadığını ortaya koymaktı.

Gereç ve Yöntemler: Bu retrospektif çalışma bir askeri hastanede yapıldı. Çalışmaya toplam 384 hasta dahil edildi. Hastalar ultrasonografik (US) olarak saptanan AOYKH'na göre iki gruba ayrıldı. Grupların sosyodemografik, biyokimyasal, histopatolojik, virolojik ve US bulguları retrospektif olarak kaydedildi. SPSS 22,0 kullanılarak istatistiksel analizleri yapıldı.

Bulgular: Tümü erkek olan hastaların yaş ortancası 26 yıl (20-40 yıl) saptandı. Hastaların %16,9'unda AOYKH tanımlandı. AOYKH olan hastaların %36,9'unda HBsAg pozitifliği saptandı. AOYKH olan ve olmayan hastalar arasında HBsAg pozitifliği açısından istatistiksel olarak önemli fark saptanmadı (p=0,661). HBsAg pozitif hastaların %13,2'sinde, HBsAg negatif hastaların %20,3'ünde AOYKH belirlendi. HBsAg pozitif ve negatif hastalar arasında AOYKH açısından önemli fark bulunmadı (p=0,158). HBsAg pozitif hastalarda γ-glutamil transferaz, HBsAg negatif hastalarda yaş, alanin transaminaz ve aspartat transaminaz AOYKH varlığı ile ilişkili en önemli faktörler olarak belirlendi.

Sonuç: Bu çalışmada HBsAg pozitifliğinin genç hastalarda AOYKH gelişimi ile ilişkili olmadığını, HBV ve AOYKH birlikteliğinin rastlantısal olabileceğini saptadık.

Anahtar Kelimeler: Alkolik olmayan yağlı karaciğer hastalığı, kronik hepatit B, ultrasonografi

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Introduction

There are 400-500 million hepatitis B virus (HBV) carriers worldwide (1). Although the prevalence differs accross the various regions, 4% of the population in Turkey are carriers of HBV (2), with a rate of 2.8% in 20 year-old people (1).

Fatty liver disease may be observed as a comorbidity in patients with HBV infection. Hepatosteatosis, or fatty liver, is defined as an accumulation of triglycerides in the cytoplasm of hepatocytes. If hepatosteatosis occurs without heavy alcohol use, the term of non-alcoholic fatty liver disease (NAFLD) is used. NAFLD may be observed in the form of simple fat deposition as well as non-alcoholic steatohepatitis (NASH) with inflammation identified, and cirrhosis may develop (3).

The incidence of NAFLD and chronic hepatitis B (CHB) varies according to region. Various studies conducted in Brazil and in Taiwan have reported the incidence of NAFLD as 10-56% (4,5), while studies conducted in Turkey have reported the incidence as 39-42% (6,7). NAFLD does not contribute to the progression of HBV infection (8,9). Cindoruk et al. (10) showed that NAFLD had no negative effect on treatment success in patients with hepatitis B. It is difficult to establish a cause and effect relationship between HBV and NAFLD (5,7). Does the relationship between HBV infection and NAFLD occur for the same reasons in other segments of society, and if so, is the association coincidental?

The objective of this study was to determine the factors associated with the presence of NAFLD in young persons who are hepatitis B surface antigene (HBsAg)-positive and negative, and to investigate if the coexistance of NAFLD and HBV is coincidental.

Materials and Methods

This retrospective study was conducted in a military hospital between January 1st, 2012 and June 30th, 2015. A total of 384 patients aged 20-40 years, who had undergone an abdominal ultrasonography (US) for any reason, were included in the study. Exclusion criteria were defined as positive serology for hepatitis C virus, acute hepatitis findings, liver disease due to other reasons, and regular and heavy consumption of alcohol.

Patients' age, weight, height, alanine transaminase (ALT), aspartate transaminase (AST), γ-glutamyl transferase (GGT), alkaline phosphatase, fasting blood glucose (FBG) values, US, and HBsAg outcomes were obtained from the hospital data base. Body mass index (BMI) was calculated using height and weight (weight/height^2). Hepatitis B e-antigene (HBeAg), HBV DNA values, histologic activity index (HAI) from liver biopsy outcomes, and fibrosis scores were recorded in 182 patients identified to be HBsAg-positive.

All patients were divided into two groups according to the presence of NAFLD which had been defined by US findings. Demographic and laboratory data were compared in order to evaluate their effect on development of NAFLD. In addition, all patients were further divided into two subgroups based on HBsAg positive and negative status, and NAFLD identified by US was investigated in these two groups. The subgroups were evaluated separately for the presence of NAFLD with demographic and laboratory data. Independent risk factors affecting the development of NAFLD were separately studied in all patients and the subgroups.

Hepatic US was performed with GE Logiq 5 PRO ultrasound system (GE Medical Systems - Milwaukee, WI, USA) using a convex broadband (4-10MhZ) transducer. NAFLD was graded by comparing diffusely increased echogenicity in the liver with echogenicity of the right kidney cortex. NAFLD grading was made according to the following criteria (11):

Grade 1: Diffuse increased echogenicity with normal vascular walls and normal diaphragm echogenicity.

Grade 2: Partially unclear echogenicity of intrahepatic artery/vein walls and diaphragm.

Grade 3: Echogenicity of the diaphragm wall could not be observed and posterior segment of the liver was determined with difficulty.

Liver needle biopsy was performed with a 16-gauge Menghini needle under local anesthesia. Liver parenchyma was assessed using modified KNODELL scoring system (1995 ISHAK) (12).

The Helsinki Declaration and Good Clinical Practice Guidelines were followed in all the processes of patient inclusion, data collection and analysis, and reporting. The study was approved by the Local Ethics Committee.

Statistical Analysis

Statistical analysis was carried out utilizing SPSS IBM 22.0 software. Distribution of the data was studied with the Kolmogorov-Smirnov test. Descriptive statistics were performed for each group. Normally distributed continuous variables were expressed with mean + standard deviation, non-normally distributed data median (minimum-maximum), and categorical data with number and percentage. Differences between the groups were analyzed using the student's t-test and the Mann-Whitney U test. Categorical variables were studied using the Pearson X^2 and Fisher's Exact tests. Independent risk factors for the development of NAFLD were determined by logistic regression analysis. A p value of less than 0.05 was considered statistically significant.

Results

The study included a total of 384 patients. The median age of the patients, all of whom were male, was 26 years (20-40). NAFLD was identified in 65 (16.9%) patients. Of these 65, NAFLD was defined as grade 1 in 44 (67.7%) and grade 2 in 20 (30.8%) patients, while one patient (1.5%) had grade 3 NAFLD. Demographics and laboratory values of the groups according to the presence of NAFLD are summarized in Table 1. Age, weight, BMI, and GGT values were found to be higher in patients with NAFLD compared to those without NAFLD (for each, $p<0.001$). Although the other laboratory parameters were higher in patients with NAFLD defined, the differences did not reach statistical significance (Table 1). HBsAg positivity was found in 36.9% of patients with NAFLD. It was remarkable that no statistically significant difference was found in HBsAg positivity between patients with and without NAFLD ($p=0.661$) (Table 1).

HBsAg positivity was identified in 182 (47.4%) of patients included in the study. The median HAI value of the patients was 5 (minimum-maximum: 0-14) and the median fibrosis score was 2 (minimum-maximum: 0-5). HBeAg positivity was observed in around 50%. NAFLD was found in 13.2% of HBsAg-positive

patients. There were significant differences in terms of weight (p=0.018), BMI (p=0.001), and GGT (p=0.002) according to the presence of NAFLD among the patients in this group. NAFLD was found in 20.3% of HBsAg-negative patients. In this group of patients, significant differences were found in terms of age (p=0.002), weight (p<0.001), BMI (p<0.001), ALT (p<0.001), AST (p<0.001), GGT (p<0.001), and FBG levels (p<0.001). Demographics and laboratory data of HBsAg-negative and -positive patients according to the presence of NAFLD are given in Table 2.

Among the HBsAg-positive patients, 18 patients (75%) were found to have NAFLD grade 1, 5 patients (20.8%) had grade 2, and NAFLD grade 3 was defined in 1 patient (4.2%). In HBsAg-negative patients, NAFLD was determined as grade 1 in 26 patients (63.4%) and grade 2 in 15 patients (36.6%), while none of these patients had grade 3 NAFLD. No significant difference was found in NAFLD grades between HBsAg -positive and -negative patients (p=0.158).

In the present study, only GGT in HBsAg-positive patients, and age, ALT, and AST in HBsAg-negative patients were determined as the most important factors associated with the presence of NAFLD. GGT level was found to be determining factor associated with the presence of NAFLD in HBsAg-positive patients. It is noteworthy that AST level negatively affected occurrence of NAFLD, and in patients HBsAg-negative patients, the probability of having NAFLD decreased as the level of AST increased. We found that age and ALT levels increased the odds of determination of NAFLD, and in HBsAg- negative patients, the most important factor was ALT (Table 3).

Discussion

In this study, NAFLD was found in 16.9% of all patients. We observed that NAFLD was more infrequent in CHB patients, and that HBsAg was not a significant factor in patients with NAFLD. The prevalence of NAFLD is 19.8% in our country (13), whereas in Western populations this rate has been reported to be between 20% and 30% (14). According to the Turkish data, NAFLD is found in 21.1-52% of inactive HBsAg carriers (6,15,16), and in 39% of CHB patients (7). In their study performed in Indonesia, Lesmana et al. (8) found the incidence of NAFLD to be 29.9%. Poortahmasebi et al. (17) in their study performed in Iranian patients reported that 44.4% of CHB patients had NAFLD. Similar to our study, Wang et al. (5) also reported that the incidence of NAFLD in HBsAg-positive patients was similar to that in HBsAg-negative patients. In addition, it has been reported in a meta-analysis examining fatty liver in HBV patients that the incidence of NAFLD among HBV patients was similar to that of the general population (18). It is noteworthy that the incidence of NAFLD in our study was lower compared to the data from our country and other countries, and that HBsAg positivity did not increase the incidence of NAFLD. This result suggests that NAFLD identified in CHB patients might be coincidental.

In the present study, NAFLD grade was found to be lower in HBsAg-positive patients than in HBsAg-negative subjects. In their study, Uyanıkoğlu et al. (6) found that 73% of HBV-infected patients had grade 1, 21% had grade 2, and 6% had grade 3 fatty liver. In their study, Korkmaz et al. (16) found that 61% of inactive hepatitis B carriers had grade 1, 35% had grade 2, and 4% had grade 3 fatty liver. It has been noticed in previous studies that low grade fatty liver is common among HBV patients. Similarly, low grades of NAFLD found in our study suggest that the progression of fattening level might be reduced in young people by several regulations, such as lifestyle changes and diet. Furthermore, in our study, there was no correlation established between HBsAg positivity and NAFLD grade, supporting that this association is coincidental.

It has been demonstrated in several studies that NAFLD is more common in men and in advanced age groups (13,19). In the present study, HBsAg-negative patients were in a young age group, and the incidence of NAFLD was significantly higher in older patients in the same group. Previous studies have reported that male gender and advanced age are significant factors in HBV patients (6,7,15,16,17). However, in our study, we could not find a similar correlation with age in patients with positive HBsAg.

There were also obese patients in our study. It is known that the prevalence of NASH which is the advanced stage of NAFLD, is six times higher in obese patients compared to persons within

Table 1. Demographic data, virological and biochemical results of patients (median/minimum-maximum)

Variable	All patients (n=384)	NAFLD positive (n=65, 16.9%)	NAFLD negative (n=319, 83.1%)	p value
Age (year)	26 (20-40)	31 (20-40)	25 (20-40)	<0.001±
Height (cm)	1.77 (1.59-1.94)	1.78 (1,62-1.94)	1.77 (1.59-1.93)	0.997
Weight (kg)	76.5 (50-115)	80 (60-103)	75 (50-115)	<0.001±
BMI (kg/m^2)	24.7 (17.4-35.5)	26 (19.6-34.6)	24 (17.3-35.5)	<0.001±
ALT (0-45 U/L)*	51 (11-553)	55 (15-207)	50 (11-553)	0.095
AST (0-35 U/L)*	31.5 (15-188)	32 (16-75)	31 (15-188)	0.494
GGT (0-55 U/L)*	24 (7-114)	29 (13-112)	23 (7-114)	<0.001±
ALP (38-155 U/L)*	72 (38-236)	72 (45-150)	72 (38-236)	0.903
FBG (74-106 mg/dL)* mean + SD	93.17±8.86	94.69±9.74	92.86±8.65	0.162
HBsAg (n/%)				
Positive	182 (47.4)	24 (36.9)	158 (49.5)	0.661
Negative	202 (52.6)	41 (63.1)	161 (50.5)	

*Normal values, NAFLD: Non-alcoholic fatty liver disease, BMI: Body mass index, ALT: Alanine transaminase, AST: Aspartate transaminase, GGT: γ-glutamyl transferase, ALP: Alkaline phosphatase, FBG: Fasting blood glucose, SD: Standard deviation, HBsAg: Hepatitis B surface antigene, ±: Statistically significant

a normal weight range (19). Numerous studies have shown that BMI is an important factor associated with NAFLD in patients with hepatitis B and in other segments of society without HBV infection (4,7,8,9,10,13,17,20). Likewise, in our study, we found that weight gain, and thus BMI, is crucial in terms of the presence of NAFLD and makes a significant difference in NAFLD development.

In the present study, GGT was significantly high both in HBsAg-positive and -negative patients detected to have NAFLD. The importance of GGT levels in patients with hepatitis B differs among the studies. Korkmaz et al. (16) mentioned that GGT is important for NAFLD, while Altıparmak et al. (7) and Nau et al. (20) found no significant difference in terms of GGT levels.

In a study by Wang et al. (5) with HBsAg positive and negative patient groups, risk factors contributing to NAFLD were triglycerides, BMI, and insulin resistance. In our study, the only determinative factor for CHB patients was GGT. In these patients, the control for abdominal US would be reasonable for NAFLD in the case of high GGT levels. Among patients with negative HBsAg, those with high ALT levels and advanced age may require evaluation for NAFLD.

The number of studies comparing the incidence of NAFLD in CHB patients and those with negative HBsAg is limited (5). Furthermore, no study was found in the literature screening that investigates this comparison in between 20-40 years old patients. We believe that our results will make a contribution to the literature because of the young patient population we studied, and the comparison of our data between HBsAg positive and negative groups. We selected histopathologically-proven CHB patients in order to investigate the presence of additional disease which might contribute to the existing damage at certain levels in the liver tissue. This feature distinguishes our study from the other studies. However, our study has some limitations. We had difficulty in finding similar studies with which we could compare our data. Our patient population consisted solely of male patients because of military hospital. Lack of data for both

Table 2. Demographic data, virological and biochemical results of patients with hepatitis B virus (median/minimum-maximum)

Variable	HBsAg positive patients (n=182)			HBsAg negative patients (n=202)		
	NAFLD positive (n=24, 13.2%)	NAFLD negative (n=158, 86.8%)	p value	NAFLD positive (n=41, 20.3%)	NAFLD negative (n=161, 79.7%)	p value
Age (year)	21 (20-40)	21 (20-33)	0.078	35 (23-40)	30 (22-40)	0.002±
Height (cm)	1.74 (1.62-1.94)	1.75 (1.59-1.90)	0.109	1.79 (1.67-1.88)	1.78 (1.65-1.93)	0.348
Weight (kg)	80 (60-103)	73 (50-115)	0.018±	81 (67-93)	77 (60-97)	<0.001±
BMI (kg/m^2) mean + SD	26.3±3.11	23.9±3.38	0.001±	25.5±1,64	24.3±1.68	<0.001±
ALT (0-45 U/L)*	86 (47-207)	81 (43-553)	0.927	44 (15-125)	24 (11-107)	<0.001±
AST (0-35 U/L)*	43.5 (30-75)	43 (24-188)	0.538	28 (16-65)	23 (15-63)	<0.001±
GGT (0-55 U/L)*	39 (20-112)	26.5 (8-79)	0.002±	28 (13-74)	20 (7-114)	<0.001±
ALP (38-155 U/L)*	81 (47-150)	80 (40-236)	0.944	67 (45-131)	65 (38-159)	0.422
FBG (74-106 mg/dL)* mean + SD	88.21±9.02	91.79±10.09	0.102	98.49±8.06	93.90±6.84	0.001±

*normal values, NAFLD: Non-alcoholic fatty liver disease, HBsAg: Hepatitis B surface antigene, BMI: Body mass index, ALT: Alanine transaminase, AST: Aspartate transaminase, GGT: γ-glutamyl transferase, ALP: Alkaline phosphatase, FBG: Fasting blood glucose, SD: Standard deviation, ┼: Statistically significant

Table 3. The factors associated with the presence of non-alcoholic fatty liver disease

	B	Wald	p value	OR	CI
HBsAg positive patients					
GGT (U/L)	0.040	7.719	0.005	1.041	1.012-1.071
Constant	-7.523	17.36	<0.001	0.001	
Cox and snell R2	0.103				
Nagelkerke R2	0.190				
Overall percentage	0.874				
HBsAg negative patients					
Age (year)	0.154	9.819	0.002	1.166	1.059-1.284
ALT (U/L)	0.101	16.65	<0.001	1.106	1.054-1.161
AST (U/L)	-0.125	5.702	0.017	0.882	0.796-0.978
Constant	-18.264	14.481	<0.001	<0.001	
Cox and snell R2	0.271				
Nagelkerke R2	0.427				
Overall percentage	0.871				

BMI: Body mass index, ALT: Alanine transaminase, AST: Aspartate transaminase, GGT: γ-glutamyl transferase, OR: Odd's ratio, CI: Confidence interval, HBsAg: Hepatitis B surface antigene

genders created a limiting condition for our study. Since we did not include patients receiving treatment and inactive HBsAg carriers, we could not make any interpretation about these groups.

Conclusion

Our study found that HBsAg positivity is not correlated with the development of NAFLD in young patients, and coexistence of NAFLD with HBV might be coincidental. Weight gain might be the cause for the development of NAFLD in patients with HBV. In addition, we found predictive factors for the presence of NAFLD to be high GGT levels in HBsAg-positive patients, and age, high ALT, and high AST levels in HBsAg-negative patients. However, these results should be confirmed with additional, larger studies that include both genders.

Ethics

Ethics Committee Approval: The Helsinki Declaration and Good Clinical Practice Guidelines were followed in all the processes of patient inclusion, data collection and analysis, and reporting. The study was approved by the Local Ethics Committee, Informed Consent: It was taken.

Peer review: External and Internal peer-reviewed.

Authorship Contributions

Concept: Zehra Karacaer, Gökcan Okur, Design: Zehra Karacaer, Gökcan Okur, Data Collection or Processing: Zehra Karacaer, Gökcan Okur, Hakan Çermik, Özgür Avcı, Analysis or Interpretation: Zehra Karacaer, Gökcan Okur, Literature Search: Zehra Karacaer, Gökcan Okur, Writing: Zehra Karacaer, Gökcan Okur, Hakan Çermik, Özgür Avcı.

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Research Article

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The Frequency of Hepatitis B Virus, Hepatitis C Virus and Human Immunodeficiency Virus Infections among Patients with Schizophrenia in a Mental Health Hospital in Turkey

Türkiye'de Bir Ruh Sağlığı Hastanesinde Şizofreni Hastalarında Hepatit B Virüs, Hepatit C Virüs ve İnsan İmmün Yetmezlik Virüsü Sıklığı

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ABSTRACT

Objective: Several studies have demonstrated that psychiatric patients are at increased risk for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections compared the general population. The aim of this study was to determine the frequency of HBV, HCV and HIV infections among patients with schizophrenia in Elazığ Mental Health Hospital in Turkey.

Materials and Methods: Screening tests for HBV, HCV and HIV have been routinely performed in patients with schizophrenia. Hepatitis B surface antigen (HBsAg), anti-hepatitis B surface (anti-HBs), anti-HCV and anti-HIV tests were performed by the ELISA technique.

Results: Four hundred and eighty-nine patients with schizophrenia in the mental health hospital were screened for HBsAg, anti-HBs, anti-HCV and anti-HIV. The study population was consisted of 409 male and 80 female patients. Overall seroprevalence was detected as 6.5% for HBsAg, 41.5% for anti-HBs and 0.2% for anti-HCV. All patients were found to be anti-HIV-negative.

Conclusion: This study showed that the frequency of HBV, HCV and HIV infections among patients with schizophrenia was no higher than in the general population. Screening for blood-borne pathogens at the time of admission to the hospital is an important strategy to identify infected residents. Furthermore, hepatitis B vaccination schedule should be extended to include all the community.

Keywords: Hepatitis B, hepatitis C, human immunodeficiency virus, schizophrenia

ÖZ

Amaç: Birçok çalışma, genel popülasyon ile karşılaştırıldığında psikiyatri hastalarının hepatit B virüs (HBV), hepatit C virüs (HCV) ve insan immün yetmezlik virüsü (HİV) enfeksiyonları için artmış risk altında olduğunu göstermiştir. Bu çalışmanın amacı, Türkiye'de Elazığ Ruh Sağlığı ve Hastalıkları Hastanesi'nde şizofreni hastalarında HBV, HCV ve HİV enfeksiyon sıklığını belirlemekti.

Gereç ve Yöntemler: HBV, HCV ve HİV için tarama testleri, şizofreni hastalarında rutin olarak uygulanmıştır. Hepatit B'nin yüzey antijeni (HBsAg), anti hepatit B yüzey antikoru (anti-HBs), anti-HCV ve anti-HİV testleri, ELISA yöntemi ile çalışıldı.

Bulgular: Ruh sağlığı hastanesindeki dört yüz seksen dokuz şizofreni hastası, HBsAg, anti-HBs, anti-HCV ve anti-HİV için tarandı. Hasta popülasyonu, 409 erkek ve 80 kadın hastadan oluştu. Genel seroprevalans, HBsAg için %6,5, anti-HBs için %41,5 ve anti-HCV için %0,2 olarak tespit edildi. Anti-HİV, tüm hastalarda negatif saptandı.

Sonuç: Bu çalışma, şizofreni hastalarında HBV, HCV and HİV enfeksiyon sıklığının genel popülasyondan daha yüksek olmadığını göstermiştir. Hastaneye başvuru sırasında kan yoluyla bulaşan patojenler için tarama yapılması, enfekte bireyleri belirlemek için önemli bir stratejidir. Ayrıca, hepatit B aşılama programı tüm toplumu kapsayacak şekilde genişletilmelidir.

Anahtar Kelimeler: Hepatit B, hepatit C, insan immün yetmezlik virüs, şizofreni

Karabulut N. The Frequency of Hepatitis B Virus, Hepatitis C Virus and Human Immunodeficiency Virus Infections among Patients with Schizophrenia in a Mental Health Hospital in Turkey. Viral Hepat J 2016;22:48-51

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Introduction

Preventing and managing hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections is a serious public health issue worldwide. Worldwide, 240 million people are chronically infected with HBV, accounting for more than 620.000 deaths per year. 2.35% of the world population is chronically infected with HCV, approximately 160 million people worldwide (1,2). The estimated number of persons living with HIV in the world was approximately 36.9 million at the end of 2014 (3). The prevalence of HBV, HCV and HIV infections shows variations across different geographical areas in the world. Turkey is classified as a country of intermediate endemicity for HBV and HCV infections. According to the Turkish Ministry of Health, the first HIV case in Turkey was reported in 1985, and 11.109 HIV cases were reported until the end of March 2016 (4). A vaccine against hepatitis B has been available since 1982 (5), yet a systematic vaccination policy was not adopted at that time in Turkey. Since 1998, hepatitis B vaccination has been included in the national immunization program (6).

In several studies, it has been reported that psychiatric patients have an increased risk for hepatitis B, hepatitis C and HIV infections compared the general population (7,8). Comorbidity of schizophrenia and viral diseases incurs a worse prognosis for both conditions (9). Psychiatric symptoms may increase the risk of contracting blood-borne viral infections among people with severe mental illness including those with schizophrenia. Many patients with schizophrenia have high-risk sexual behavior and inadequate knowledge about protective measures or transmission or the risks of these diseases. To stay long periods in same-sex wards in hospitals may foster high-risk same-sex activity (10). In addition, due to the use of common shaving accessories in male patients may lead to parenteral transmission of these infections. These factors may increase the risk of transmission of blood-borne infections among psychiatric patients. Screening for and prevention of sexually-transmitted infections and blood-borne viruses are neglected in this population. Determining the frequency of HBV, HCV and HIV infections among patients with schizophrenia has a significant role in designing the strategies to control the disease. Data about the prevalence of these infections among patients with schizophrenia in Turkey could not be found in the literature. Therefore, this study was conducted to determine the frequency of HBV, HCV and HIV infections among patients with schizophrenia in Elazığ Mental Health Hospital, Turkey.

Materials and Methods

The mental health hospital is a state hospital with 488 beds in the Eastern Anatolia region of Turkey. The hospital serves 18 cities in Eastern and Southeastern Anatolia. Screening tests for HBV, HCV and HIV have been routinely performed in patients admitted to the psychiatry ward. This retrospective study included 489 patients with schizophrenia (409 males, 80 females) in Elazığ Mental Health Hospital in 2015. The study was approved by the Fırat University Ethics Committee.

Laboratory Examinations

Blood samples were analyzed in the central clinical laboratory of the hospital. HBsAg, anti-HBs, anti-HCV (GBC, Taiwan, R.O.C.) and anti-HIV (DIA.PRO, Milano, Italy) tests were performed using the Triturus system (Grifols, Parets del Valles, Spain) by the ELISA method. The positive and negative controls were included each run. Specimens with a cutoff index of <1 were considered as non-reactive; cutoff index ≥1 was considered as reactive for HBsAg, anti-HCV and anti-HIV tests. Samples with below 10 mIU/mL were considered as non-reactive, and values of above 10 mIU/mL were considered as reactive for anti-HBs. Initially reactive assays were repeated in duplicate.

Statistical Analysis

Statistical analyses were performed using SSPS 20 (SPSS Inc, Chicago, IL, USA). The chi-square test was used for categorical comparisons of nominal values in different groups. The Kruskal-Wallis test was used to compare parameters among the age groups. A p value of less than 0.05 was considered statistically significant.

Table 1. The seroprevalence of hepatitis B surface antigen and anti-hepatitis B surface in the patients with schizophrenia

Characteristics			HBsAg		Anti-HBs	
		Number of subjects	Positive patients n (%)	p	Positive patients n (%)	p
Overall		489	32 (6.5)		203 (41.5)	
Gender	Male	409	28 (6.8)	0.541	164 (40.1)	0.151
	Female	80	4 (5.0)		39 (48.8)	
Age groups	<20	10	0 (0)	0.645	8 (80)	<0.001
	20-29	59	3 (5.1)		22 (37.3)	
	30-39	136	12 (8.8)		37 (27.2)	
	40-49	146	7 (4.8)		74 (50.7)	
	50-59	98	8 (8.2)		42 (42.9)	
	>60	40	2 (5.0)		20 (50)	

HBsAg: Hepatitis B surface antigen, Anti-HBs: Anti-hepatitis B surface

Results

The mean age of 489 patients with schizophrenia was 42.46±11.29 years (range: 15-74 years).

As shown Table 1, 32 HBsAg-positive cases were reported, and the seroprevalence of HBsAg was determined as 6.5%. There was no significant difference in the frequency of HBsAg between genders. Additionally, no significant difference was found in the seroprevalence rate of HBsAg between age groups.

203 patients were detected to be anti-HBs-positive, and the seroprevalence rate was 41.5%. There was no significant difference in the seroprevalence rate of anti-HBs between genders. The highest seroprevalence was detected in the age group under 20 years ($p<0.001$) (Table1).

The seroprevalence rate of Anti-HCV was 0.2%. A 63-year-old male patient was detected to be anti-HCV-positive. In addition, anti-HIV was negative in all the patients.

Discussion

Psychiatric patients do not have awareness about risk factors facilitating transmission of blood-borne viruses, and protective measures against these infections. Several studies have indicated that patients with mental illnesses are at an increased risk for HBV, HCV and HIV infections. Although the prevalence of HBV, HCV and HIV in the general was found to be 4.9%, 1.8% and 0.32-0.42% respectively, it was 23.4%, 19.6% and 5.2-22.9% among individuals with severe mental illness. The prevalence of blood-borne viral infections in people with serious mental illness has been found to be higher than in the general population in the U.S.A (11). A meta-analysis of studies of the prevalence of HIV, HBV and HCV in people with severe mental illness published between 1980 and 2015 found that the prevalence of blood-borne viral infections in people with serious mental illness was consistently higher than in the general population in regions with a low prevalence of blood-borne viruses, such as the USA and Europe, and on par with the general population in regions with high general prevalence such as Africa for HIV and Southeast Asia for HBV and HCV (12). A study conducted in patients with chronic schizophrenia in Taiwan revealed that the seroprevalence of HBsAg and anti-HCV was 10.4% and 1.9%, respectively. The authors reported that this prevalence among patients with schizophrenia was not higher than in the general population in Taiwan (13).

The prevalence of HBV, HCV and HIV among 5.227 psychiatric patients in Elazığ Mental Health Hospital between 2011 and 2013 was reported in our previous study. According to this study, overall seroprevalence was 4.08% for HBsAg, 42.19% for anti-HBs and 0.69% for anti-HCV. HIV was not detected among the subjects of the study (14). In 2009, the seroprevalence of HBsAg, anti-HBs and anti-HCV in 1343 patients in a psychiatric hospital in the western part of Turkey was detected as 2.7%, 30.5% and 1.8%, respectively (15). The present study has demonstrated that the frequency of HBsAg, anti-HBs and anti-HCV among patients with schizophrenia was 6.5%, 41.5% and 0.2%, respectively. All the patients were anti-HIV-negative. The frequency of HBV infection among patients with schizophrenia was not higher than in the general population. Additionally, the prevalence of HCV and HIV in the general population in Turkey is already low. In our hospital, various preventive measures such as continuous surveillance, education of the psychiatric patients regarding transmission of blood-borne infections, and improving hospital conditions for patients are being taken.

The most dramatic decline in HBsAg positivity was observed among patients with schizophrenia under the age of 20 years. Anti-HBs positivity was detected in 80% of this group. In Turkey, hepatitis B vaccination was included in the national immunization program in 1998, and infants have been vaccinated with three doses. Adults in the risk groups are also vaccinated at their request (16,17).

This study has several limitations. The tests separating the active and chronic infection could not be analyzed. In addition, the test showing the evidence of previous HBV vaccination or past HBV infection in anti-HBs-positive patients could not be performed. Finally, it was a retrospective study, and risk factors associated with transmission of HBV and HCV in the patients could not be determined.

This study showed that the frequency of HBV, HCV and HIV infections among patients with schizophrenia was not higher than in the general population. Screening for blood-borne pathogens including HBV, HCV and HIV at the time of admission to the hospital is an important strategy to identify infected residents. Hepatitis B vaccination schedule should be extended to include all the community. Lastly, strategies targeting at risk reduction will be important to prevent further spread of blood-borne infections among psychiatric populations.

Ethics

Ethics Committee Approval: This retrospective study included 489 patients with schizophrenia (409 males, 80 females) in Elazığ Mental Health Hospital in 2015. The study was approved by the Fırat University Ethics Committee.

Peer-review: External and Internal peer-reviewed.

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Research Article

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Red Cell Volume Distribution Width to Platelet Ratio is an Important Predictor of Liver Fibrosis and Cirrhosis in Chronic Hepatitis B

Eritrosit Dağılım Genişliği Trombosit Oranı Kronik Hepatit B'de Karaciğer Fibrozisi ve Sirozun Önemli Bir Belirleyicisidir

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ABSTRACT

Objective: In recent years, a lot of non-invasive tests have been examined for estimating the severity of liver fibrosis in patients with chronic hepatitis B (CHB). We aimed to evaluate the role of simple and valuable platelet-derived indices in estimating the stage of fibrosis and cirrhosis in patients with CHB.

Materials and Methods: A total of 434 biopsy-proven naive CHB patients were included in the study. Liver biopsy samples were examined using the ISHAK scoring system. Age, sex, complete blood count parameters and the stage of fibrosis of the patients were recorded. The patients were evaluated according to the severity of fibrosis (stage 0-2: No fibrosis/mild fibrosis and stage 3-6: Significant fibrosis) and the presence of cirrhosis (stage 0-4: No cirrhosis, stage 5-6: Cirrhosis).

Results: Of the 434 patients included in the study, 252 (58.1%) were men and 182 (41.9%) were women. The mean age of the patients was 42.7±12.2 years. Significant liver fibrosis was found in 108 (24.9%) patients and cirrhosis in 43 (9.9%) patients. In dual analysis, alterations in many platelet-derived parameters were observed. Receiver operating characteristic curve analysis revealed that red blood cell distribution width to platelet ratio index was the highest area under the curve value (0.777) in predicting significant liver fibrosis and the cutoff value was 0.0814, sensitivity was 56% and specificity was 87%.

Conclusion: Platelet-derived indices may play an important role in observing the progression of liver fibrosis and cirrhosis. Platelet ratio index is significantly increased in advanced liver fibrosis in patients with CHB, and can be defined as independent predicting factor in liver fibrosis.

Keywords: Chronic hepatitis B, platelet-derived indices, liver fibrosis, cirrhosis

ÖZ

Amaç: Son yıllarda, kronik hepatit B (KHB) hastalarında fibrozis şiddetini tahmin etmek için bir çok non-invaziv test çalışılmıştır. Biz basit ve kullanışlı olan platelet kökenli indekslerin kronik hepatit B (KHB) hastalarında fibrozis düzeyi ve siroza gidişte rolünü araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmaya biyopsi ile kanıtlanmış 434 naif KHB hastası dahil edildi. Karaciğer biyopsi örnekleri İSHAK skorlama sistemi kullanılarak incelendi. Yaş, cinsiyet, tam kan sayım parametreleri ve fibrozis evresine ait hasta verileri kaydedilmiştir. Hastalar, fibrozis şiddeti (evre 0-2: Fibrozis yok/hafif ve evre 3-6: Önemli fibrozis) ve siroz varlığı (evre 0-4: Siroz yok, evre 5-6: Siroz) açısından değerlendirilmiştir.

Bulgular: Çalışmaya dahil edilen 434 hastanın, 252'si (%58,1) erkek, 182'si (%41,9) kadındı. Hastaların yaş ortalaması 42,7±12,2 idi. Hastaların 108'inde (%24,9) önemli karaciğer fibrozisi, 43'ünde (%9,9) siroz saptandı. İkili analizlerde platelet temelli birçok parametrede anlamlı değişkenlikler saptanmıştır. Alıcı işletim karakteristiği analizi ile yaptığımız değerlendirmede eritrosit dağılım genişliği/trombosit indeksini önemli karaciğer fibrozisini öngörmede en yüksek eğri altında kalan alan değeri (0,777) olarak saptadık ve cutoff değerini 0,0814, duyarlılığı %56, özgüllüğü %87 olarak belirledik.

Sonuç: Platelet kökenli indeksler, karaciğer fibrozisi ve siroza ilerlemeyi gözlemlemede önemli bir rol oynayabilir. Trombosit indeksi, KHB hastalarının ilerlemiş karaciğer fibrozisinde anlamlı olarak daha yüksektir ve karaciğer fibrozisinin bağımsız belirleyen faktörü olarak tanımlanabilir.

Anahtar Kelimeler: Kronik hepatit B, trombosit kökenli indeksler, karaciğer fibrozisi, siroz

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Introduction

Hepatic fibrosis is a part of structural and functional changes observed in chronic liver disease (CLD). In the past 25 years, studies have revealed numerous cellular and molecular mechanisms leading to hepatic fibrogenesis. From the biological perspective, fibrogenesis is a dynamic process characterized by accumulation of fibrillar extracellular matrix as a consequence of continuous derangement and remodeling related to chronic tissue damage (1). The stage of fibrosis is among the most significant prognostic factors in CLD regarding development of cirrhosis and liver-related complications. Liver biopsy has been traditionally considered as the gold standard in assessment of liver fibrosis tissue damage in patients with CLD. Along with technical problems, such as length of biopsy material, problems about experience of the doctor obtaining biopsy samples and pathologist assessing the sample and risk of potential life-threatening complications limit the use of invasive procedures (2,3). Preferring non-invasive, cost-effective and simple methods while evaluating severity of liver fibrosis may be a more rational choice due to the above mentioned reasons. In recent years, for the evaluation of CLD severity, several non-invasive markers have been developed as an alternative to liver biopsy (4). However, the methods used were rather based on studies about chronic hepatitis C (CHC) (5). In the literature, inconsistent conclusions were reached in estimating states of liver fibrosis in CHB patients. Recently, various models were proposed for CHB patients, however, to use these models in daily practice seems difficult because they are rarely used biological markers or require specific software programs to make some calculations (6). Thus, there is an unmet need for reliable, simple and routine methods predicting liver fibrosis (7).

Hematological complete blood count (CBC) parameters are the most utilized laboratory tests in clinical practice. CBC includes parameters, such as white blood cell (WBC), red blood cell (RBC) and platelet (PLT) as well as some morphological indices. PLT has a primary role in liver inflammation mechanisms. It has a positive role in liver regeneration, but may have negative effect on the liver by causing immune-mediated injury (8). There is a negative correlation between progression of liver fibrosis and PLTs (7). In numerous studies, effectiveness of these parameters and indices on predicting outcome of the disease and risk of mortality was investigated (9,10,11,12).

In recent years, several studies employing platelet-derived indices (PDIs) in order to predict fibrosis level in CHB patients were carried out with inconsistent results and both number of cases and investigated parameters were limited. In this study, we aimed to determine effectiveness of simple and easily available complete blood parameters and PDI in CHB patients in predicting significant fibrosis and cirrhosis.

Materials and Methods

Study Population

This was a retrospective case-control study evaluating chronic hepatitis B virus (HBV)-infected cases. The study included 434 naive CHB patients followed up after diagnosis and treatment in Department of Infectious Diseases and Clinical Microbiology, Bezmialem Vakıf University Faculty of Medicine, İstanbul, Turkey between January 2011 and December 2015. Patients, aged 18 years and older, having hepatitis B surface antigen positivity for more than six months, liver biopsy evaluated by using ISHAK scoring system, having estimable CBC parameters before biopsy and treatment were included in this study. Patients having coinfection of hepatitis C virus (HCV), human immunodeficiency virus and hepatitis D virus, autoimmune disorders, metabolic liver disease, cardiac diseases, atherosclerotic diseases, hypertension, vascular diseases, chronic pulmonary diseases, renal diseases, chronic infections, diabetes mellitus, rheumatic diseases, splenectomy, hematological diseases, malignancy, pregnancy, taking drugs such as antidiabetics, hyperlipidemics, antihypertensives, warfarin, heparin, and aspirin were excluded from this study. The patients were evaluated according to severity of fibrosis (stage 0-2: No/mild fibrosis, stage 3-6: Significant fibrosis) and presence of cirrhosis (stage 0-4: No cirrhosis, stage 5-6: Cirrhosis). Case-control groups were also constructed according to the stage of liver fibrosis. Case groups were described as patients having advanced stages of fibrosis (stage 3-6 and stage 5-6). Control groups were described as patients having stage 0-2 and stage 0-4 scores.

Laboratory Analysis

Pre-treatment serum HBV-DNA was measured by using real-time polymerase chain reaction method (BioRad iCycler iQ System, Qiagen DNA isolation kit, Hilden, Germany: Detection limit: 20 IU/mL). CBC analysis was done by Advia 2120 (Siemens Healthcare Diagnostics, Siemens, Dublin, Ireland, Advia CDC Timepac CN free No. T01-3627-01) full automated hematological analyzer. All blood samples were analyzed within an hour. WBC, neutrophil (NEU), lymphocyte (LYM), RBC, mean corpuscular volume (MCV), hemoglobin, red blood cell distribution width (RDW), PLT, mean PLT volume (MPV), PLT distribution width (PDW), plateletcrit (PCT) along with estimated PLT-derived indices RPR, mean platelet volume to platelet ratio (MPR), PLT to WBC ratio (PWR), NEU to PLT ratio (NPR), and PLT to LYM ratio (PLR) were included in the evaluation.

Histological Evaluation

Ultrasound-guided liver biopsy was obtained by fully automated biopsy needle from at least five portal ducts as minimum 1.5 cm liver tissue for diagnosis. The samples were prepared by using hematoxylin-eosin and Masson's trichrome stains on formalin-fixed paraffin-embedded liver tissue. Liver biopsy was performed in all patients and biopsy samples were examined using the ISHAK scoring system.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software (version 17, SPSS, Inc., Chicago, IL, USA). Conformity of continuous variables to normal distribution was evaluated by the single-sample Kolmogorov-Smirnov test. Categorical variables were expressed as percentage and number and in comparison of means, the independent-sample t-test, Mann-Whitney U test, and the Kruskal-Wallis H test were used as appropriate by considering conformity to normal distribution and number of evaluable subjects. Binary logistic regression analysis was performed using block entry approach to examine the contribution of variables in identifying the cases with severe fibrosis. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value for the variables

included in the model. The optimal cut-off values were identified by calculating the Youden index (13). All p-values were 2-sided, and values 0.05 were considered statistically significant.

Results

Patients' Characteristics

Nine hundred thirty-eight patients of the 1372 patients were excluded from the study as per exclusion criteria. 252 (58.1%; mean age: 42.7±12.2 years) of 434 subjects included in the study were male and 182 (41.9%) were female. Hepatitis B e antigen was positive in 70 (16.1%) patients. One hundred and eight (24.9%) patients had significant fibrosis (stage 3-6) and 43 (9.9%) had cirrhosis (F5-6).

Predictors of Liver Fibrosis

The relationship between significant liver fibrosis and cirrhosis and CBC parameters and PDI is shown in Table 1. WBC, NEU, LYM, RBC, PLT, PCT values were lower in significant fibrosis and presence of cirrhosis ($p<0.05$). Higher MCV was found to be associated with cirrhosis (p=0.004), but no correlation with significant fibrosis was found (p=0.106). Hemoglobin was not associated with significant fibrosis and cirrhosis. Advanced regression analysis revealed no association between PDW value and significant fibrosis (p=0.67). PLR among PDI was significantly lower in significant fibrosis (p=0.003), but there was no relationship between PDW value and presence of cirrhosis (p=0.329). With significant fibrosis and presence of cirrhosis, RPR, MPR, NPR indices were higher and PWR was lower and the relationship was statistically significant (p=0.001).

In logistic regression analysis, the association between RDW, PLT, MPV values and significant liver fibrosis was statistically significant in CHB patients (Table 2).

Evaluations performed by using ROC analysis revealed that RPR index is more valuable in predicting liver fibrosis (Table 3, Figure 1).

Discussion

The aim of this study was to find out the most valuable PDI predictive of significant fibrosis and cirrhosis to evaluate its effectiveness and develop an appropriate method by using simple, cost effective and easily available CBC tests. In our study, RPR was found to be more valuable in predicting advanced liver fibrosis compared to other PDIs. The mechanism underlying between RDW and liver fibrosis is not fully understood yet. Increase in RDW may be an indicator of iron immobilization and inflammatory stress (14). Excessive iron load and inflammation may subsequently contribute to liver fibrosis. The role of PLTs in progression of fibrosis is also not clear. However, it has been shown that in a negative correlation with PLTs, decrease in profibrogenic transforming growth factor-beta expression and increase in matrix metalloproteinase expression may alleviate liver fibrosis (15). RDW increase may be observed in CLDs and particularly in cirrhosis as a result of hemolytic anemia which is common in these conditions

Table 1. Comparison of cases with no/mild (stage 0-2) and significant fibrosis (stage 3-6), also non-cirrhosis (stage 0-4) and cirrhosis (stage 5-6)

Parameters	Severity of fibrosis			Presence of cirrhosis		
	No/mild fibrosis n=326 (75.1%)	Significant fibrosis n=108 (24.9%)	p value	Non-cirrhosis n=391 (90.1%)	Cirrhosis n=43 (9.9%)	p value
Age (years)	40.73±11.56	48.54±12.3	0.001	41.60±11.89	52.47±10.72	0.001
Gender (male)	182/326 (56)	70/108 (65)	0.10	218/391 (%56)	34/43 (%79)	0.003
WBC (103/mm^3)	6950±1513	6298±1696	0.001	6910.38±1487	5672.09±1975	0.001
NEU (103/mm^3)	3853±1176	3537±1248	0.018	3822.77±1152	3334.65±1522	0.011
LYM (103/mm^3)	2334±630	1999±700	0.001	2322.49±627	1602.32±642	0.001
RBC (106/mm^3)	4.99±0.46	4.80±0.56	0.001	4.97±0.46	4.62±0.66	0.001
MCV (fL)	86.21±4.73	87.25±6.09	0.106	86.23±5.04	88.62±5.30	0.004
Hb (g/dL)	14.34±1.6	14.01±1.8	0.669	14.31±1.57	13.77±2.12	0.684
PLT (103/mm^3)	226.53±59	167.69±63	0.001	220.07±59.68	137.47±65.53	0.001
MPV (fL)	10.50±1.11	10.57±1.25	0.590	10.51±1.14	10.63±1.21	0.484
PDW (%)	13.44±2.55	14.44±2.93	0.001	13.60±2.62	14.44±3.09	0.053
PCT (%)	0.24±0.06	0.19±0.09	0.001	0.23±0.06	0.17±0.12	0.001
RDW (%)	13.48±1.25	14.11±1.48	0.001	13.55±1.30	14.42±1.41	0.001
RPR	0.06±0.018	0.10±0.05	0.001	0.066±0.02	0.13±0.064	0.001
MPR	0.05±0.017	0.075±0.041	0.001	0.052±0.018	0.097±0.053	0.001
PWR	0.0336±0.01	0.0272±0.01	0.001	0.033±0.01	0.025±0.01	0.001
NPR	17.72±6.01	22.97±9.32	0.001	18.20±6.22	26.59±11.38	0.001
PLR	0.104±0.04	0.09±0.04	0.003	0.10±0.04	0.095±0.05	0.329

Gender values are case count (%). Other all values are mean ± SD (standard deviation). WBC: white blood cell; NEU: Neutrophil, LYM: Lymphocyte, RBC: Red blood cell, MCV: Mean corpuscular volume, Hb: Hemoglobin, PLT: Platelet, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, RDW: Red blood cell distribution width, RPR: Red blood cell distribution width to platelet ratio, MPR: Mean platelet volume to platelet ratio, PWR: Platelet to white blood cell ratio, NPR: Neutrophil to platelet ratio, PLR: Platelet to lymphocyte ratio

(16). In some studies, increasing RDW level was found to be associated with severity of disease in CHB patients (10,17). When there was a 1% increase in RDW level, risk of progressive liver fibrosis has increased by 12.1%. However, the mechanism which increases RDW level in higher stage of liver fibrosis is still not clear (18). We have determined that RDW is a significant variable in predicting advanced liver fibrosis by performing dual analysis and multivariate analysis. PLTs have a critical role in maintaining homeostasis, but are also important mediators of acute and chronic inflammatory diseases particularly following liver injury. PLTs play an important role in HBV-associated acute and chronic liver diseases by increasing accumulation of virus-specific CD8+ T cells and nonspecific inflammatory cells in liver parenchyma (19). Thrombocytopenia is a known complication of CLD and cirrhosis. PLT is used in various predictive models of liver fibrosis and cirrhosis. In a meta-analysis, it has been shown that aspartate aminotransferase (AST)-PLT ratio index (APRI) and fibrosis-4 (FIB-4) index can identify liver fibrosis in CHB with a moderate sensitivity and accuracy (20). Chen et al. (7) are the first investigators reporting an association between RDW and liver fibrosis and have reported that in the study, the most robust predictors in CHB patients namely RDW and PLT when used to get RPR have led to more accurate prediction of the risk of significant fibrosis (63.1%) and cirrhosis (73.7%) compared to AST-alanine aminotransferase (ALT) ratio (AAR), FIB-4 and APRI. Cengiz and Ozenirler (21) have determined RPR index as an independent predictor of significant and advanced liver fibrosis in 54 patients with non-alcoholic fatty liver disease (NAFLD). In a recently published study including 482 patients with chronic hepatitis B by Lee et al. (22), it was stated that when transient elastography is not available RPR index may serve as a simple method lowering the need for liver biopsy. In our study, the evaluation by using ROC analysis has revealed that RPR index had the highest area under the curve value (0.777) in predicting significant liver fibrosis with a cut off value of 0.0814, and its sensitivity was 56% and specificity was 87%. This result was consistent with other studies performed to predict severe liver fibrosis in CHB and CHC patients (7,23).

MPV and PDW are parameters measured in routine blood counts reflecting the size and the degree of difference in size of PLTs. In destructive thrombocytopenia, higher MPV levels and in hypoproliferative thrombocytopenia, lower MPV levels are observed (24). In CHB patients, IL-6 increasing with inflammation increases PLT production in bone marrow (25). High MPV levels are associated with cardiovascular diseases, cerebrovascular diseases and certain risk factors, such as mild inflammatory conditions predisposing to thrombosis (26). PDW which is a more specific marker for PLT activation may be used in differential diagnosis of PLT disorders. In a study, a positive correlation between high PDW and MPV levels and severity of vascular injury was shown (27). MPV and MPR may be used in sepsis and systemic inflammatory response syndrome studies (28). MPV was also investigated in liver diseases such as steatosis, cirrhosis and hepatitis (29). Cho et al. (30) have found in their study including 165 hepatocellular carcinoma (HCC) patients that MPR index was more relevant than MPV as an indicator of tumor presence. Karagoz et al. (10) have established MPV and RDW values as independent risk factors in predicting liver fibrosis in CHB, however, they found that PDW was not statistically significant. In our study, we also have determined significant association between MPV and MPR and prediction of severe fibrosis in CHB patients. PLR index has a significant role in predicting outcome of hepatocellular cancer. Lai et al. (31) has determined in 181 HCC patients that PLR was a good determinant of recurrence risk after liver transplantation. In our study, lower PLR index was significantly associated with fibrosis but no association was found with cirrhosis. Studies about NPR and PWR indices are very scarce in the literature. Menezes et al. (32) have reported that a PWR index of <8 during presentation in sepsis patients was associated with higher mortality in day 4 and day 28. In our study, PWR index was significantly lower in patients at cirrhosis stage. De Ferrari et al. (33) have determined that higher NPR index was independent determinant of short-term or long-term mortality in patients with myocardial infarction. In our study, NPR was found to be higher in CHB patients with advanced fibrosis. Value of PCT which is a marker of PLT activation has a tendency to increase particularly in cardiovascular diseases; it is calculated by using PCT=PLT count × MPV/10^7 formula (34). Tsai et al. (35) has concluded that lower PCT value in144 HCV patients as compared to control group was a

Tablo 2. Comparison of variables associated with the presence of significant fibrosis (stage 3-6)

Variables	Beta value	Odds ratio	95% confidence interval	p value
RDW	0.353	1.423	1.164-1.738	0.001
PLT	-0.055	0.946	0.907-0.987	0.01
MPV	-0.803	0.448	0.215-0.933	0.03
PDW	-0.023	0.978	0.880-1.085	0.67

RDW: Red blood cell distribution width, PLT: Platelet, MPV: Mean platelet volume, PDW: Platelet distribution width

Table 3. Area under receiver operating characteristic curve of platelet indices in the prediction of significant fibrosis (stage 3-6)

Indices	AUC	Cutoff	95% CI	p value	Sensitivity	Specificity	PPV	NPV
RPR	0.777	0.0814	0.723-0.831	0.001	0.56	0.87	58.7	85.8
MPR	0.735	0.0575	0.677-0.792	0.001	0.63	0.74	44.5	85.8
PWR	0.697	0.0272	0.637-0.758	0.001	0.58	0.77	45.3	84.7
NPR	0.673	21.1337	0.612-0.733	0.001	0.53	0.77	43.2	83.1
PLR	0.621	0.0632	0.558-0.684	0.001	0.29	0.91	52.5	79.4

AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, RPR: Red blood cell distribution width to platelet ratio, MPR: Mean platelet volume to platelet ratio, PWR: Platelet to white blood cell ratio, NPR: Neutrophil to platelet ratio, PLR: Platelet to lymphocyte ratio

significant finding. Also in our study, lower PCT value in CHB patients with advanced liver fibrosis was considered statistically significant. Studies about PCT values are scarce and we assume that more detailed and comprehensive studies are needed.

Study Limitations

There are some limitations in this study. First, we have not investigated other etiologic factors increasing RDW levels such iron or vitamin B12 deficiency. Secondly, we could not investigate possible variation due to genotype, because in our country genotype testing for CHB patients is not a routine practice. Thirdly, age-platelet index, gamma-glutamyl transpeptidase (GGT) to platelet ratio, platelet-age-phosphatase-alpha-fetoprotein-AST index, Goteburg University Cirrhosis Index, platelet-spleen diameter ratio, AST-platelet-GGT-alpha-fetoprotein index, Forn's index, AAR, APRI, FIB-4, fibro-quotient and other PDIs were not used in this study. Fourthly, time regarding laboratory results could not be standardized, because we accepted the most recent laboratory results obtained before the biopsy without stating a time interval. Fifthly, the size of the sample was limited because it was a single-center study. Sixthly, specificity of RPR index is high but its sensitivity is lower. Due to these reasons, we think that more comprehensive multi-centered studies about prediction of fibrosis in CHB patients including comparison of these PDIs and other non-invasive methods are warranted.

Conclusion

Our study helped us obtaining significant information about the use of CBC in prediction of CHB prognosis. Along with RDW and platelet count being cost-effective, easily calculable RPR index was determined as having the most effective predictive value. This information may help us reducing the number of irrelevant liver biopsy.

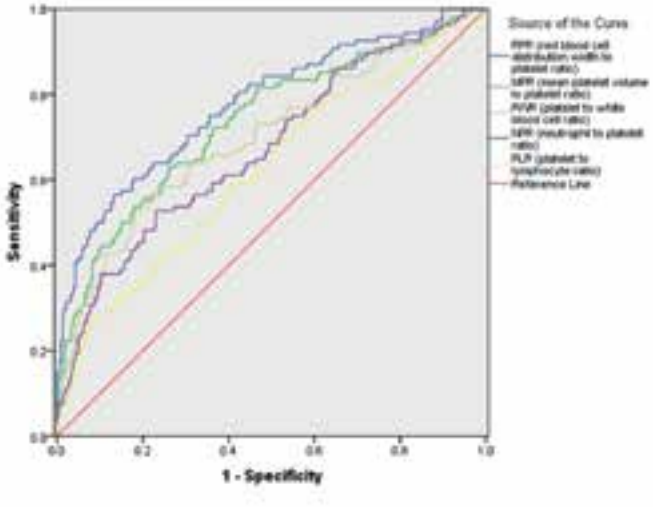

Figure 1. Receiver operating characteristic curves of platelet-derived indices in predicting significant fibrosis (stage 3-6) at optimum cut-off point
RPR: Red blood cell distribution width to platelet ratio, Mean platelet volume to platelet ratio, PWR: Platelet to white blood cell ratio, NPR: Neutrophil to platelet ratio, PLR: Platelet to lymphocyte ratio

Ethics

Ethics Committee Approval: The study was approved by Bezmialem Vakıf University Ethic Committee for Clinical Research (2015/7588).

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Concept: İsmail Necati Hakyemez, Design: İsmail Necati Hakyemez, Turan Aslan, Data Collection or Processing: İsmail Necati Hakyemez, Bülent Durdu, Analysis or Interpretation: Sibel Bolukçu Literature Search: İsmail Necati Hakyemez, Bülent Durdu, Writing: İsmail Necati Hakyemez, Turan Aslan.

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Research Article

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Telaprevir-based Triple Therapy for Retreatment of Chronic Hepatitis C Patients with Genotype Four Followed in Our Clinic

Kliniğimizde İzlenen Genotip Dört ile Enfekte Kronik Hepatit C'li Hastalarda Telaprevir Tabanlı Üçlü Tedavi

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ABSTRACT

Objective: Telaprevir-based triple therapy for chronic hepatitis C virus (HCV) patients with genotype 4 is not recommended potently by the guidelines. There are few studies in the literature related to this issue. This study showed the antiviral activity and safety of telaprevir-based regimens in the treatment of treatment-experienced genotype 4 chronic HCV-infected patients.

Materials and Methods: This retrospective study consisted of 12 genotype 4 HCV-infected patients. All patients received 12 weeks of telaprevir in combination with 24 weeks of pegylated interferon (PEG-IFN) alpha and ribavirin (RBV).

Results: The sustained virological response (SVR) rate was six of 12 (50%). Notably, the rate of SVR in prior relapsers was 75% (6 of 8). SVR could not be achieved in non-responders.

Conclusion: Telaprevir, a potent HCV NS3-4A protease inhibitor, has been used as monotherapy and in combination with PEG-IFN/RBV in patients infected with genotype 1, 2 and 3 HCV. Limited clinical data suggest that telaprevir has activity against genotype 4 HCV. In this study, it was observed that the addition of telaprevir to the standard regimen had a greater activity on treatment relapse patients with genotype 4.

Keywords: Chronic hepatitis c, telaprevir, genotype 4

ÖZ

Amaç: Telaprevir bazlı üçlü tedavi ders kitaplarındaki önerilere dayanılarak genotip 4 hepatit C virüslü (HCV) hastalarda önerilmemektedir. Literatürde genotip 4 HCV pegile interferon/ribavirin (PEG-İFN/RBV) tedavi deneyimli ve kalıcı viral yanıt alınamamış hastalarda telaprevir bazlı üçlü tedavinin etkinliğini belirleyen az sayıda çalışma bulunmaktadır. Çalışmada bu konuda literatüre katkıda bulunmayı amaçlanmıştır.

Gereç ve Yöntemler: Çalışma retrospektif olarak dizayn edilmiş olup daha önceden PEG-İFN/RBV tedavisi almış ve nüksetmiş ya da yanıtsız olarak değerlendirilmiş 12 genotip 4 HCV enfeksiyonlu hasta alındı. Hastaların tedavi bitiminden 24 hafta sonra kalıcı viral yanıtları (KVY) kaydedildi.

Bulgular: KVY'li tüm hastaların altısı (%50) alındı. KVY'si alınan hastaların tamamı PEG-İFN/RBV tedavisi sonrası nüks hastalar olduğu görüldü. PEG-İFN/RBV tedavisine cevapsız olan dört hastanın hiçbirinde KVY alınamadı.

Sonuç: Telaprevir, etkili bir NS3-4A proteaz inhibitörü olup PEG-İFN/RBV ile ya da tek başına genotip 1, 2, 3 HCV hastaların tedavisinde kullanılmaktadır. Genotip 4'te kullanımına yönelik yapılan çalışmalar sınırlıdır. Çalışmamız, telaprevir bazlı PEG-İFN/RBV tedavisinin genotip 4 relaps 15 hastalarında KVY'yi önemli oranda arttırdığını göstermektedir.

Anahtar Kelimeler: Kronik hepatit c, telaprevir, genotip 4

Beştepe Dursun Z, Çelik İ. Telaprevir-based Triple Therapy for Retreatment of Chronic Hepatitis C Patients with Genotype Four Followed in Our Clinic. Viral Hepat J 2016;22:58-61

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Introduction

Hepatitis C virus (HCV) infection is a major global health issue. HCV is genetically heterogeneous with 6 major HCV genotypes (1). HCV-4 is the cause of approximately 20% of the 170 million cases of chronic hepatitis C in the world (2).

In Turkey, chronic HCV infection is an important health problem. Genotype 1 accounts for 68-94% and genotype 4 (G4) accounts for 36% of HCV infections. The prevalence of HCV G4 has been increased in recent years (3,4). HCV genotype is considered to be an independent factor affecting the response to interferon treatment (5). Therefore, analysis of the genotype of HCV is also important in regulating response and duration of the treatment (5,6).

The features of G4 and management strategies for patients infected with this genotype are not equally easily developed as for genotypes 1, 2, and 3 (2).

Telaprevir (TVR), an orally bioavailable inhibitor of the nonstructural 3/4A HCV protease (2), combined with pegylated interferon plus ribavirin (PEG-IFN/RBV) substantially improved rates of sustained virologic response (SVR) in patients who were treated previously for HCV infection (7,8).

In patients infected with HCV G4, triple-combination with TVR had better results compared to PEG-IFN/RBV dual therapy (9).

For G4 HCV patients in whom SVR is not achieved with PEG-IFN/RBV, re-treatment options are limited to re-exposure to the same medications, with potential modification of the dose or duration of the regimen.

It was proposed to assess efficacy, safety and side effects of triple therapy and especially TVR in our HCV patients who were diagnosed with G4 (subtype 4d) and previously received PEG-IFN/RBV treatment.

This was an uncommon clinical trial to evaluate the antiviral activity of TVR in G4 HCV-infected patients.

Materials and Methods

Patients

This retrospective study consisted of 12 patients who were followed up in our clinic between January 2013 and February 2014. Patients, who were anti-HCV- and HCV RNA-positive and presented with the signs and symptoms of chronic hepatitis diagnosed by liver biopsy, were included in the study. All the patients were infected with HCV alone. No other accompanying infectious diseases were found. Liver biopsies were scored with reference to the ISHAK staging system (10). Those with F4-5 fibrosis were considered having cirrhosis. Patients classified as child-pugh B and C were considered as having cirrhosis.

We considered TVR in combination with PEG-IFN alpha-2a or 2b plus RBV in patients who had relapse after an initial response and not responded or partially responded to previous therapy. The results of TVR plus PEG-IFN/RBV treatment were recorded at baseline, 4th rapid virological response (RVR), 12th early virological response (EVR), 4th through 12th (eRVR) and 24th and 48th week [end of treatment viral response (EOTVR)] virologic response and SVR after 24th week at the end of treatment.

The study were retrospective, at the same time ethical approval is expected for the meeting by the Erciyes University of Local Ethics Committee.

Results

The mean age of the patients was 55±10.8 years (range: 31-73). Among HCV patients infected with HCV G4, the diagnosis was confirmed by a liver biopsy before screening for the study. Four patients with compensated liver cirrhosis were eligible. All treatments were discontinued in patients with a decrease in HCV ribonucleic acid (RNA) level of less than 2 log10 from baseline to week 12. Only one patient had no EVR, and his treatment was stopped. Eleven patients completed their treatment. The demographic characteristics of patients are shown in Table 1.

Responses of the patients are shown in Table 2. SVR was achieved in 50% of patients (6 out of 12).

The number of prior relapsers was 8, and the SVR rate among them was 75% (6 out of 8). One of these patients showed an improvement between the 20th and 24th weeks of treatment. This patient had no RVR, but he had only EVR. One of the relapsers had no RVR, EVR and SVR.

Four patients were non-responders to previous therapy and two of them had RVR and entecavir, but they had an improvement between the 20th and 24th weeks of treatment. SVR was not achieved in any of the nonresponders. One of these patients died because of liver failure at the 20th week of treatment. He had RVR, eRVR and EVR, but liver decompensation occurred in this patient (Figure 1).

Discussion

G4 HCV is uncommon in the U.S. and Europe, although this genotype is most prevalent in Middle East and North Africa. G4 HCV was classified as "difficult-to-treat," because it had not been extensively studied in clinical trials of protease inhibitor therapies formerly (11,12). In a study performed in Kayseri, G4 was observed in 24 of 100 patients (13), and the suboptimal SVR rates achieved with Peg-IFN/RBV in a study done by Kamal and Nasser (2).

Table 1. Demographic characteristics of the patients

Age (mean ± SD)	55±10.8
Gender	
Male	5 (42%)
Female	7 (58%)
Cirrhosis	4 (33%)
Relapse	3 (75%)
Nonresponder/partial responder	1 (25%)
Previous therapy	
Naïve	None
Relapse	8 (67%)
Nonresponder/partial responder	4 (33%)
Baseline HCV RNA (log10 IU/mL) minumum-maximum	5.76±0.6 (4.75-6.72)

SD: Standard deviation, HCV: Hepatitis C virus, RNA: Ribo nucleic acid

However, recently, there are some studies about protease inhibitor used in G4 HCV-infected patients. In these studies, SVR was achieved with ledipasvir in combination with sofosbuvir or ombitasvir, paritaprevir and ritonavir in about 90% of subjects. However, it is not possible to reach these new drugs in all countries.

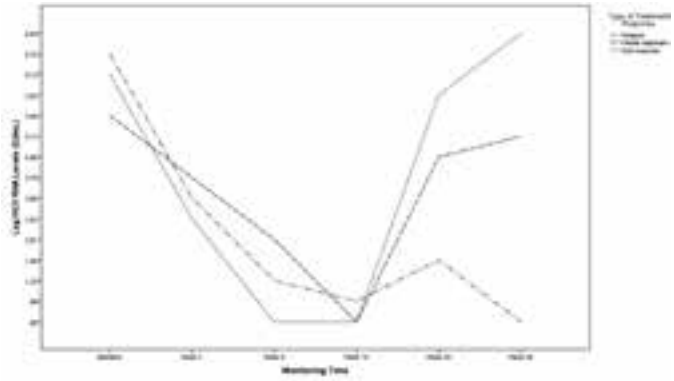

Figure 1. Type of treatment response

Table 2. Response rates of all of the patients	
Previous relapsers	
Undetectable viral load at 4th week (RVR)	6/8 (75%)
Undetectable viral load at 4th through 12th (eRVR)	6/8 (75%)
Undetectable viral load at 12th week (EVR)	6/8 (75%)
End of treatment viral response	6/8 (75%)
Viral response after the end of treatment's 24th week (SVR)	
All patients	6/8 (75%)
Patients with undetectable viral load at 4th week	6/6 (100%)
Patients with bridging fibrosis or cirrhosis‡	2/3 (66%)
Virologic failure	2/6 (33%)
No response or partial response to previous therapy	
Undetectable viral load at 4th week (RVR)	2/4 (50%)
Undetectable viral load at 4th through 12th (eRVR)	2/4 (50%)
Undetectable viral load at 12th week (EVR)	4/4 (100%)
End of treatment viral response	2/4 (50%)
Viral response after the end of treatment's 24th week (SVR)	
All patients	0/4 (0%)
Patients with undetectable viral load at 4th week	0/2 (0%)
Patients with bridging fibrosis or cirrhosis	0/1 (0%)
Virologic failure	4/4 (100%)

Several studies indicate that in G1 HCV patients who were treated with protease inhibitors-based triple drugs, SVR rates were higher than in those who received Peg-IFN/RBV treatment (8). In a study which included HCV patients with G4, triple-combination therapy with TVR had better results compared to PEG-IFN/RBV therapy. Antiviral activity was found to be higher in the triple-combination group compared to the other groups (9). In our cities a study conducted by Aygen et al. (14), nine patients who had G4 HCV were evaluated. These patients had undetectable HCV RNA levels at 24th week. In this study, SVR rates were not evaluated, but EOTVR response rate was found to be 80.2%.

In our study, the SVR was 50% (6 out of 12). SVR rates were higher in patients who achieved RVR and eRVR during treatment. RVR and eRVR rates may indicate if the patient will achieve SVR with this treatment.

Moreover, the SVR was higher in relapsers than in nonresponders. Most of the relapsers (75%; 6 out of 8) achieved SVR. All SVR-achieved relapsers achieved RVR and eRVR as well. Although 2 out of 4 nonresponders achieved RVR and eRVR, SVR could not be obtained in those patients. On 12th weeks of treatment, 11 patients had undetectable HCV RNA levels. Five patients showed improvement over the 20th week.

The determination of HCV genotypes and subtypes is very important to indicate the response to antiviral therapy (5,6).

With the introduction of specific HCV-1 protease inhibitors boceprevir and TVR in 2011, HCV-4 became the "most difficult to treat" genotype especially in patients previously treated with partial responder (15,16). All patients who included in our study were G4d (13).

Conclusion

Although this study was with a small sample size, it has showed that TVR plus PEG-IFN/RBV has highly antiviral activity (SVR: 50%) against HCV G4 in relapsers and nonresponders to standard therapy. This treatment may be preferred in patients who have relapse after standard therapy.

This triple treatment can attain SVR better than standard therapy but the combination treatment could lead to some serious side effects from interferon and ribavirin. Recently, there have been profound changes in the treatment of hepatitis C. New medicines are quite successful and have fewer side effects, and they are promising drugs for overcoming the disease (17). However it is not always possible for everyone to reach these drugs. TVR treatment should be considered when other drugs can not be reached.

Ethics

Ethics Committee Approval: The study were retrospective, at the same time ethical approval is expected for the meeting by the Erciyes University of Local Ethics Committee, Informed Consent: Consent form was filled out by all participants.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Zehra Beştepe Dursun, Concept: Zehra Beştepe Dursun, Design: Zehra Beştepe Dursun, İlhami Çelik, Data Collection or Processing: Zehra Beştepe Dursun, Analysis or Interpretation: Zehra Beştepe Dursun, İlhami Çelik,

Literature Search: Zehra Beştepe Dursun, Writing: Zehra Beştepe Dursun.

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Seroprevalence of Hepatitis B Virus, Hepatitis C Virus and HIV among Health Care Staff in a State Hospital

Bir Devlet Hastanesindeki Sağlık Çalışanlarının Hepatit B Virüs, Hepatit C Virüs ve HIV Seroprevalansları

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Keywords: Hepatitis B virus-hepatitis C virus-human immunodeficiency virus, health care staff, seroprevalence
Anahtar Kelimeler: Hepatit B virüs-hepatit C virüs-insan immün yetmezlik virüs, sağlık çalışanı, seroprevalans

Alay H, Çelik N, Göktuğ Kadıoğlu B, Çınar Tanrıverdi E, Parlak E, Battal Mutlu F, Özkurt Z. Seroprevalence of Hepatitis B Virus, Hepatitis C Virus and HIV among Health Care Staff in a State Hospital. Viral Hepat J 2016;22:62-64

Dear Editor;

As a nature of their profession, health-care professionals are at risk of exposure to infectious agents originating from infected patients and physical environment. Among these infectious agents, hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) play a major role. According to WHO data 3 million (two million of those to HBV, 0.9 million to HCV and 170.000 to HIV) health care staff are exposed to viral agents as a result of injury by contaminated medical equipments (1). The aim of this study was to determine HBV, HCV and HIV seroprevalence among health-care staff in Nenehatun Obstetrics and Gynecology Hospital and to enroll the hepatitis B surface antigen (HBsAg) (-)/anti-HBs (-) health care staff to vaccination program.

Records of 493 health-care staff who were working between January 2011 and January 2016 were retrospectively evaluated. Blood samples collected from the subjects were analyzed for HBsAg, anti-HBs, anti-HBc immunoglobulin (Ig) G, anti-HCV by enzyme-linked immunosorbent assay (ELISA) (Rose, Hitachi). Anti-HIV reactive samples detected in the laboratory at our hospital were considered suspicious for HIV infection and, for confirmation, new blood samples were taken and sent to Ankara Refik Saydam Hıfzısıhha Institute.

A total of 493 health-care professionals (156 male, 337 female; mean age 36 years) were included in the study. Blood samples were taken for HBAg, anti-HBs, anti-HBc IgG and anti-HCV testing. HBsAg-reactive patients were also investigated other hepatitis B markers. Of the 493 health-care professionals, 25 were doctor (5.07%), 212-nurse (43%), 60-technician (12.2%), 85-cleaning staff member (17.2%), 43-medical secretary (8.7%), 42-administrative staff (8.5%), 15-security guards (3.04%), and 11 were food handler (2.2%).

Among occupational groups, HB immunity was highest in nurses (95.8%) and least in the group named as other group (secretary, administrative staff, security guards and food

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handlers) (53.2%). Evaluation of HBsAg reactivity distribution in health-care staff showed that 5 cleaning staff members, and 1 (1.2%) technician had HBsAg reactivity. HBsAg reactivity was not detected among doctors and nurses (Table 1). Anti-HCV and anti-HIV reactivity were not detected in any subject.

Evaluation of immunity against HBV showed that there were vaccine-induced immunity in 95.8% of midwives-nurses, in 92% of doctors, in 75.3% of technicians, in 58.1% of cleaning staff and in 53.2% in the group named as other group (secretary, administrative staff, security guards and food handlers). Seven health-care staff had innate immunity to HBV (Table 2).

Several studies indicated that seroprevalence of viral hepatitis among health-care professionals was between 0.4 and 3.6% (2,3). Hospital conditions, number of health-care staff, and occupational group distribution may be the cause of the differences in these rates. In our study, we found the rate of HBsAg reactivity as 1.2%. One of 6 HBsAg reactivity detected personnel had started to receive chronic hepatitis treatment. The other 5 personnel were accepted as HB carrier and were recommended follow-up visits 2 times in a year.

Screening and follow-up of health-care staff regularly provide early detection and treatment of chronic hepatitis. In that way, we can prevent fatal complications, such as cirrhosis and hepatocellular carcinoma.

Table 1. Distribution of hepatitis B virus results among occupational groups

Occupational groups	HBsAg (+)		Anti-HBs (+)	
	n	%	n	%
Doctor (n=25)	-	-	23	92
Midwife-nurse (n=212)	-	-	203	95.8
Technician[1] (n=85)	1	1.2	64	75.3
Cleaning staff (n=43)	5	11.6	25	58.1
Other[2] (n=111)	-	-	59	53.2
Total (n=493)	6	1.2	374	75.9

[1]Laboratory, x-ray and anesthesia technicians
[2]Secretary, administrative staff, security guards and food handlers
HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B

The prevalence of anti-HBs reactivity among health-care professionals in our country has been reported to be 17.9-52.9% (4). However, in our study, we determined that it was 75.9%. We found total anti-HBc reactivity in only 7 persons. We assume that the reason for the high rate of vaccine-induced immunity was due to regular screening for viral hepatitis and HIV markers and vaccination of seronegative health-care workers.

The doctors (92%) and mid-wives-nurses (93.8%) had the highest vaccination rate. The lowest vaccination rate was in the group named as the other (secretary, administrative staff, security guards and food handlers). Not contacting to patient directly and fear and unwillingness to receive vaccine were the reason for the low vaccination rate in this group. Hundred nineteen personnel without HB immunity were included in HBV vaccination program.

The frequency of HCV infection in the general population ranges between 0% and 3%. Studies in our country showed similar results (3,4). In our study, we did not detect anti-HCV reactivity.

Similar to our results, many studies in our country have not detected anti-HIV reactivity among health-care staff (2,3).

All health-care professionals are at risk of blood borne diseases. Studies from different regions of our country reported different seroprevalence rates. It is observed that there were different vaccination rates also in the same hospital (2,3,4,5). In our study, the rates were consistent with the data in our country. Education of health-care professionals about the risk of blood-borne diseases will increase the awareness. Since HB is preventable with effective vaccines, screening of the hepatitis markers in all health care staff, vaccination of nonimmunized persons, taking standard precautions to reduce the risk of transmission via direct contact with patients, using personal protective equipments, performing education programs about blood-borne diseases are essential. In addition, screening programs will enable early treatment and follow-up of infected health-care personnel and prevent complications associated with those diseases. Further comprehensive seroprevalence studies across the country are warranted.

Table 2. Distribution of immunity against hepatitis B virus among occupational groups

Occupational groups	Natural immunity		Vaccine induced immunity		Nonimmunity	
	n	%	n	%	n	%
Doctor (n=25)	-	-	23	92	2	8
Midwife-nurse (n=212)	4	1.8	199	93.8	9	4.2
Technician[1] (n=85)	1	1.2	63	74.1	20	23.5
Cleaning staff (n=43)	-	-	25	58.1	13	30.2
Other[2] (n=111)	2	1.8	57	51.4	52	46.8
Total (n=493)	7	1.4	367	74.4	119	24.1

[1]Laboratory, x-ray and anesthesia technicians
[2]Secretary, administrative staff, security guards and food handlers

Ethics

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Authorship Contributions

Concept: Handan Alay, Design: Handan Alay, Neslihan Çelik, Data Collection or Processing: Berrin Göktuğ Kadıoğlu, Esra Çınar Tanrıverdi, Fatma Battal Mutlu, Analysis or Interpretation: Zülal Özkurt, Literature Search: Emine Parlak, Writing: Handan Alay.

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Seroprevalence Rates of Hepatitis B Surface Antigen, Anti-Hepatitis C Virus and Anti-Human Immunodeficiency Virus ½ Certain Risk Groups

Belirli Risk Gruplarında Hepatit B Yüzey Antijeni, Anti-Hepatit C Virüsü ve Anti-İnsan İmmün Yetmezlik Virüsü ½ Seroprevelans Oranları

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Keywords: Hepatitis B surface antigen, anti-hepatitis C virus, anti-human immunodeficiency virus ½, seroprevelance, risk groups
Anahtar Kelimeler: Hepatit B yüzey antijeni, anti-hepatit C virüsü, anti-insan immün yetmezlik virüsü ½, seroprevelans, risk grupları

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Dear Editor;

Hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are the causes of serious viral infections affecting millions of people worldwide. Every aspect of the issue, such as modes of transmission, laboratory detection, treatment, economical burden of the diseases, etc., is one of the major concerns of the modern medicine. Diabetics, pregnant women, hemodialysis patients and cancer patients constitute high-risk groups for exposure to these infections and chronicity due to impaired or decreased immune systems, high proportion of interventional procedures, parenteral treatments and transfusions (1). It is obvious that development of the above mentioned viral infections in these immunocompromised patients also may result in more serious clinical presentations and may increase the risk for chronic infections compared to the normal population. Tracking of seroprevelance rates of viral agents provides the necessary epidemiologic data for the health-care providers together with the patients and their relatives about these infections. In this retrospective study, we have aimed to evaluate the seroprevelance rates in high-risk patients and to improve awareness of prone population on both sides of the health service.

We have determined the levels of serum hepatitis B surface antigen (HBsAg), anti-HCV and, anti-HIV ½ by chemiluminescence microparticle immunoassay method (i1000/2000, Abbott, USA) in high-risk populations during a one-year period between March 2015 and March 2016 to determine the seroprevalence rates of HBV, HCV and, HIV. S/Co levels of <0.9 were accepted as negative and S/Co levels of ≥1.1 were accepted as positive. Serum samples with a S/Co value between 0.9 and 1.1 were assigned as borderline; such samples were retested and evaluated accordingly. Seroprevalence rates of HBV, HCV and HIV are listed in the Table 1.

We have figured out that HBsAg seropositivity was below the average among cancer patients, hemodialysis patients and pregnant women compared to the other studies concerning the high-risk populations in our country, however, HBsAg seropositivity in diabetic patients was higher than the average of the studies (2,3,4,5). Diabetic patients use pocket glucose measurement devices and insulin injectors throughout their lives. These procedures possess risk of transmission of viral infections via repeated use of disposable instruments and sharing these devices and injectors with others. These patients should be educated in terms of transmission of viruses together with other infectious agents and should be warned not to share personal devices.

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Serum anti-HCV levels were also found to be below the average in hemodialysis patients, pregnant women and diabetics. Anti-HCV seroprevelance in cancer patients were similar to the rates reported in similar studies in our country (2,3,4,5).

Although not as common as HBV and HCV infections in our country -but increasing at worrying rate-, anti-HIV ½ were detected as compatible with data from other such studies, except for pregnant women, among whom Anti-HIV ½ seroprevalence rates were low (2,3,4,5).

Tracking serotrends for infectious viral agents especially in high risk-groups is important, not only for epidemiological purposes but also purposing appropriate vaccination policies, infection control procedures and early diagnosis of the diseases. Preventive measures should include safe medical interventions together with education of the patients and relatives. By this way, health-care providers may also have increased awareness to protect themselves from iatrogenic transmissions of such contiguous viral agents.

Table 1. Seroprevelance rates of hepatitis B virus, hepatitis C virus and human immunodeficiency virus in high-risk patient groups

		Seropositivity rates		
Risk groups		**HBsAg**	**Anti-HCV**	**Anti-HIV½**
Cancer patients	n	13/549	3/549	0/469
	%	2.4	0.6	0
Hemodialysis patients	n	6/144	2/144	0/131
	%	2	1	0
Pregnant women	n	113/5885	8/5885	-
	%	1.92	0.136	-
Diabetics	n	17/178	4/181	0/63
	%	9.5	2.2	0

HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

Ethics

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Authorship Contributions

Concept: Kerem Yılmaz, Mehmet Köroğlu, Design: M. Koroglu, Mustafa Altındiş, Data Collection or Processing: Tayfur Demiray, Kerem Yılmaz, Analysis or Interpretation: Tayfur Demiray, Kerem Yılmaz

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Liver Biopsy is the Gold Standard at Present, How about Tomorrow?

Karaciğer Biyopsisi Halen Altın Standart, Peki Gelecekte?

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Keywords: Viral hepatitis, liver biopsy, non-invasive tests
Anahtar Kelimeler: Viral hepatit, karaciğer biyopsisi, non-invaziv testler

Afyon M. Liver Biopsy is the Gold Standard at Present, How about Tomorrow? Viral Hepat J 2016;22:67-68

Dear Editor;

Assessment of severity of liver disease in patients with chronic hepatitis has always been a challenge for the clinician. Liver biopsy is still considered the gold standard for this purpose. However, although rare, apart from severe complications such as bleeding, biliary perforation and peritonitis, pneumothorax or death, it has some other drawbacks including inaccurate staging due to sampling errors (needle biopsy samples only 1/50.000 of the liver), lack of standardization of staining, observer-dependent diagnostic variations (inter or intra observer), and financial burden (1,2,3,4). Moreover, patients undergoing liver biopsy may require hospitalization, thus, more than 90% of complications are likely to happen during the first 24 hours after biopsy (3). Also, in patients with chronic viral hepatitis, repeated biopsies for defining the therapy response or predicting prognosis in the posttreatment follow-up period may be another problem (4). For these reasons, there are attempts searching non-invasive predictive models to substitute liver biopsy (2,3,4).

Hence, we wanted to specify non-invasive modalities predicting the degree of liver disease, particularly fibrosis, and their advantages and disadvantages in a summary. Indeed, certain non-invasive modalities, including direct or indirect serum markers and imaging tools are available for determining fibrosis degree in patients with viral hepatitis, particularly hepatitis C virus infection (2,3,4).

Imaging methods evaluating liver stiffness, such as acoustic radiation force impulse, cross-sectional imaging, 2D-shear wave elastography, ultrasound-based transient elastography (TE) or magnetic resonance elastography can accurately assess the degree of liver fibrosis, but access to these techniques and their costs can be defined as drawbacks of the radiological tests (2,4). Additionally, TE, the most widely accepted method, cannot be implemented in patients with narrow intercostal spaces or in obese individuals (2,4).

Aside from imaging tools, serum markers, indirect or direct, may be the other options to evaluate liver fibrosis (2,3,4). Indirect serum markers, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), international normalized ratio, γ-glutamyl-transpeptidase, total bilirubin, γ2-macroglobulin, apolipoprotein A1, haptoglobin, cholesterol and platelet count or indices, singly or especially in a combination including age-platelet index, AST-to-ALT ratio, AST-to-platelet ratio index (APRI), Forns' index, fibrosis index based on four factors, Fibrotest, Fibroindex, Lok index, King's score and Goteborg University Cirrhosis Index have been evaluated in many studies with questionable results (2,3,4).

Furthermore, hepatic matrix metabolism markers, reflecting matrix accumulation (fibrogenesis) or degradation (fibrolysis), as direct markers including type IV collagen, hyaluronic acid, laminin, transforming growth factor beta 1, YKL-40, metalloproteinases or tissue inhibitors of metalloproteinases have been found to be useful in predicting fibrogenesis (2,3,4).

While direct serum markers are not routinely available in clinical practice, indirect serum markers are cheaper and allow a more widespread use (4). Accordingly, the World Health Organization guidelines recommend APRI score for defining severity of fibrosis in resource-limited countries (5). Moreover, a combination of non-

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invasive tests, particularly when they include TE and Fibrotest, has been demonstrated to improve accuracy (2).

As a conclusion, it is a fact that liver biopsy is still the gold standard for the diagnosis of chronic viral hepatitis despite several drawbacks, but in the future, it may change because of several studies showing non-invasive tests to become increasingly precise in predicting no, mild or advanced fibrosis in patients with viral hepatitis (2,3,4).

Ethics

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