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E-ISSN: 2147-2939

Viral Hepatitis Journal

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August 2018
2
Volume 24

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Online Publishing Date: August 2018
E-ISSN: 2147-2939
International scientific journal published quarterly.

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AIM AND SCOPE

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

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

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

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

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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, processing or publication charges. Any processes and submissions about the journal can be made from the website: http://viralhepatitisjournal.org/. Archive of the journal is also available at this website. Manuscripts should be submitted online from https://mc04.manuscriptcentral.com/viralhepatj.

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

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

SCIENTIFIC POLICIES

Scientific and Ethics Responsibility

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MANUSCRIPT PREPARATION

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

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

Short Announcements

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

• 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 and the main text should not exceed 2000 words.

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

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

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

ARTICLE SECTIONS

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

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

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

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

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

• Turkish keywords 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 keywords. The main text should consist of introduction, case report, discussion, acknowledgment, conclusion and references. The entire text should not exceed 5 pages (A4, formatted as specified above).

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 keywords. Source of all citations should be indicated. The entire text should not exceed 25 pages (A4, formatted as specified above).

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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 1000 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. 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:

• All figures, pictures, tables and graphics should be cited at the end of the relevant sentence.

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 Crossref Similarity Check powered by "iThenticate" software. Results indicating plagiarism may result in manuscripts being returned or rejected.

Checklist for Submitted Articles:

Articles must be complete. They must include the following:

• Cover Letter

• 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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CONTENTS

Doi: 10.4274/vhd.2018.2.0001
Viral Hepatitis Journal 2018;24(2):24

Saddening Truth of Hepatitis D Infection

Hepatit D Enfeksiyonunun Üzücü Gerçeği

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The hepatitis D (Delta) virus (HDV), which was discovered late in the 1970s, is the smallest virus of human virology. Since it needs hepatitis B virus for its infectivity, it is also called as defective pathogen. The other important feature distinguishing HDV from other satellite viruses is its ability to independently replicate (1,2).

It is thought that the mechanism of HDV infection's damage to the liver is immune mediated along with cytopathic effects. There are still unenlightened aspects of its pathogenesis. HDV infection is defined as coinfection or superinfection based on the condition of accompanying HBV infection.

Our country is regarded as a medium endemic region in terms of HDV infection. It is observed that anti-HDV positivity rate is higher in Eastern and Southeastern Anatolia regionswhile significant epidemiological differences exist between regions. Anti-HDV positivity was found to be 2.39% in hepatitis B surface antigen-positive patients in our society's bus project (3). In a meta-analysis, 20% of patients with chronic HBV and 32.5% of patients with cirrhotic cases were reported to have anti-HDV positivity (4).

In this issue, Yalçın and Yalçın (5) call attention to the younger age of onset of infection and the severity of the disease in patients with HDV infection. The study evaluates 220 patients' data and particularly the histopathological findings are noted. The most severe and rapidly progressive form of chronic viral hepatitis is chronic hepatitis D. Within 5 to 10 years, it causes cirrhosis in 70% of the cases. Risk of cirrhosis is three times higher than patients with HBV mono-infection.

Treatment options for HDV infection are limited and unfortunately cure cannot be achieved with current therapies. The goal of treatment is to suppress HDV replication, which is shown by the inability to detect HDV RNA in serum. The effectiveness of interferon therapy is limited. Pegylated interferons are the current recommended treatment regimen with limited success rates (6). Treatment should continue for at least one year. Given that restricted use of pegylated interferon in cirrhosis, liver transplantation remains the only option. Thus, it is clear that new treatments are urgently needed.

As pointed out by Yalçın and Yalçın (5), what stands out in our country for chronic hepatitis D where limited treatment options exist is young cirrhotic stage patients. As HDV depends on HBV, prevention can be achieved with hepatitis B vaccination. From this point of view, the importance of HBV vaccine becomes clearer. Particularly in the Eastern and Southeastern Anatolian Regions where both HDV and hepatitis B virus prevalences are high, hepatitis B vaccination studies should be carried out intensively.

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Güner R, Hasanoğlu İ. Saddening Truth of Hepatitis D Infection. Viral Hepat J. 2018;24:24.

Research Article

25

Doi: 10.4274/vhd.2017.0016
Viral Hepatitis Journal 2018;24(2):25-42

Assessment of Quality of Life of Patients with Chronic Hepatitis B and C Treated with Pegylated Interferon-alpha

Kronik Hepatit B ve Hepatit C'de Pegile İnterferon-alfa Tedavisi Alan Hastalarda Yaşam Kalitesinin Değerlendirilmesi

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ABSTRACT

Objectives: It was aimed to evaluate health-related quality of life of patients with non-cirrhotic chronic hepatitis B (CHB) and chronic hepatitis C (CHC) during interferon therapy with the standard short form-36 (SF-36).

Materials and Methods: This study included all patients who attended the Atatürk University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology and outpatient clinics for treatment between June 2008 and June 2010 and met the inclusion criteria. A socio-demographic data questionnaire and SF-36 were administered in all subjects before the interferon therapy and in the third and sixth months of the treatment.

Results: Before the treatment, vitality/energy (p=0.01) and general health (p=0.01) scores in patients with CHB were lower than in controls. In the sixth month of the therapy, physical function (p=0.03), role physical (p=0.011), role emotional (p=0.003) and vitality/energy (p=0.005) scores were significantly lower than in controls. There was a significant difference in physical function (p=0.006), role physical (p=0.006), role emotional (p=0.001) and vitality/energy (p=0.000005) scores before the treatment and physical function (p=0.006), role physical (p=0.013), role emotional (p=0.001), vitality/energy (p=0.000005) and mental health (p=0.041) scores in the third month of the treatment and physical function (p=0.000008), social function (p=0.005), role physical (p=0.0000008), role emotional (p=0.000007), mental health (p=0.001) and vitality/energy (p=0.000005) scores in the sixth month of the treatment between patients with CHC and controls.

Conclusion: Providing guidance and counseling to patients with CHB and CHC about their illness and side effects of the drugs will increase health-related quality of life of patients and will adapt them to their treatment.

Keywords: Chronic hepatitis B, chronic hepatitis C, health-related quality of life, interferon therapy

ÖZ

Amaç: Non-sirotik kronik hepatit B (KHB) ve kronik hepatit C'li (KHC) hastalarda interferon tedavisi süresince kısa form 36 (SF-36) standart formunu kullanarak sağlıkla ilgili yaşam kalitesini değerlendirmek amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya Haziran 2008 - Haziran 2010 tarihleri tarihleri arasındaki 2 yıllık süre boyunca Atatürk Üniversitesi Tıp Fakültesi, Enfeksiyon Hastlıkları ve Klinik Mikrobiyoloji Anabilim Dalı'na ve polikliniğine başvuran ve çalışmaya dahil edilme kriterlerini karşılayan olgular alındı. Çalışmaya dahil edilen tüm olgulara, interferon tedavisi öncesinde, tedavinin üçüncü ayında ve tedavinin altıncı ayında, sosyo-demografik veri formu ve SF-36 ölçeği uygulandı.

Bulgular: KHB'li hastaların tedavi öncesi enerji (p=0,01) ve genel sağlık (p=0,01) skorlarını; tedavinin altıncı ayında fiziksel fonksiyon (p=0,03), fiziksel rol (p=0,011), emosyonel rol (p=0,003) ve enerji (p=0,005) skorlarını kontrol grubuna göre anlamlı düzeyde daha düşüktü. KHC'li hastaların tedavi öncesi fiziksel fonksiyon (p=0,006), fiziksel rol (p=0,006), emosyonel rol (p=0,001) ve enerji (p=0,000005) skorlarında; tedavinin üçüncü ayında fiziksel fonksiyon (p=0,006), fiziksel rol (p=0,013), emosyonel rol (p=0,001), mental sağlık (p=0,041) ve enerji (p=0,000005) skorlarında; tedavinin altıncı ayında ise fiziksel fonksiyon (p=0,000008), sosyal fonksiyon (p=0,005), fiziksel rol (p=0,0000008), emosyonel rol (p=0,000007), mental sağlık (p=0,001) ve enerji (p=0,000005) skorlarında kontrol grubuna göre anlamlı düzeyde farklı olduğu saptanmıştır.

Sonuç: Hastalara hastalıkları ve ilaçların yan etkileriyle ilgili rehberlik ve danışmanlık hizmetlerinin verilmesi hastaların yaşam kalitelerini artırıp, tedavi uyumunu sağlayacaktır.

Anahtar Kelimeler: Kronik hepatit B, kronik hepatit C, sağlıkla ilgili yaşam kalitesi, interferon tedavisi

Alay H, Özden K, Erol S, Çelik N, Parlak E, Parlak M. Assessment of Quality of Life of Patients with Chronic Hepatitis B and C Treated with Pegylated Interferon-alpha. Viral Hepat J. 2018;24:25-42.

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Introduction

The two most common viruses capable of causing chronic infection in the liver and associated complications are hepatitis B virus (HBV) and hepatitis C virus (HCV) (1). These are also the most important causes of chronic hepatitis in Turkey and other regions of the world. According to the World Health Organization, approximately 350-400 million people worldwide carry the virus and 1-2 million people a year die of HBV infection or complications (2). HCV infection is a widespread and severe health problem worldwide. The global prevalence of HCV infection is 3%, and 210 million people are infected (3). Quality of life is a subjective concept, and difficult to define and measure. Chronic liver disease is generally asymptomatic, but may exhibit systemic symptoms such as fatigue, nausea, pruritus, lack of appetite and psychological disorders. A significant impairment in health-related quality of life (HRQoL) may occur in this patient group (4). The majority of studies of HRQoL in chronic viral hepatitis have been concerned with HCV infection, while the number of studies concerning HBV infection is limited. Several studies of patients infected with HCV have determined a significant decrease in HRQoL compared to controls (5,6). Interferon alpha (IFN-α) is the first cytokine produced by recombinant DNA technology and is used in the treatment of numerous malignant and non-malignant diseases. Diseases treated using IFN-α include hepatitis B and C. Quality of life of patients with chronic hepatitis B (CHB) and chronic hepatitis C (CHC) under IFN therapy is known to be adversely affected (4). The purpose of this study was to evaluate HRQoL scores of naive CHB and CHC patients in the infectious diseases and clinical microbiology clinic before pegylated IFN (PEG-IFN) therapy and at the 3rd and 6th months of treatment and to investigate the effect of IFN therapy on quality of life by comparing these with the scores of healthy controls.

Materials and Methods

Research Type and Sample

Twenty-eight treatment-naive patients with HBV infection with alanine aminotransferase (ALT) levels twice as high as normal for 6 months, hepatitis B surface antigen (HBsAg)+, hepatitis B e antigen (HBeAg)+/-, with HBV-DNA $\geq 10^4$ copies/mL and no clinical findings of cirrhosis, and 23 non-cirrhotic CHC patients, anti-HCV+, with determinable HCV-RNA levels, presenting to and treated in the infectious diseases and clinical microbiology clinic between June 2008 and June 2010 were included in this prospective clinical study. Fifty-one subjects with no underlying chronic disease were enrolled as the control group. All cases were selected from among individuals aged 17-69 years.

The participants were informed about the study at interviews before commencement, and informed consent was received from all. The study was approved by Atatürk University Faculty of Medicine Ethics Committee (approval number: 65/2008). A socio-demographic data questionnaire was used in order to determine subjects' socio-demographic and disease characteristics, and the 36-Item Short Form-36 (SF-36) Health Survey was administered in order to measure quality of life. The face-to-face interview technique was used for data collection. The forms were administered verbally by a researcher, and the subjects were asked to indicate the option best matching their own circumstances.

Definitions Used in the Research

Patient group: Treatment-naive non-cirrhotic patients with HBV infection, with an at least 2-fold increase in ALT levels in the previous 6 months, HBsAg+, HBeAg+/-, HBV-DNA $\geq 10^4$ copies/mL with polymerase chain reaction (PCR) and with necroinflammatory activity ≥4 and/or fibrosis ≥2 in liver biopsy, and naive patients diagnosed with chronic non-cirrhotic HCV infection, anti-HCV+ and with HCV-RNA capable of determination with PCR were included in the study. Patients with chronic HBV and HCV infection were started on PEG-IFN α-2a therapy.

Control group: Subjects with no underlying chronic disease.

Socio-demographic Data Form

A socio-demographic form consisting of nine questions was employed to determine subjects' sex, marital status, number of children, place of residence, education level, and occupation.

The 36-Item Short Form Health Survey

The SF-36 was developed by the Rand Corporation for assessing HRQoL (7). The form has been translated into Turkish and its validity and reliability have been confirmed (8,9). The scale is a generic, self-report outcome measure. It consists of 36 items measuring eight domains-physical functioning, social functioning, physical role limitations, emotional role limitations, mental health, energy/vitality, bodily pain and general health perception. It can evaluate the positive aspects of health status, as well as negative aspects (10). The SF-36 scoring requires a separate guideline. Subdomain score calculation can be performed with a series of procedures (10). Scores range from 0 (worst possible health) to 100 (best possible health), with higher scores indicating a better quality of life. All sections are scored independently (7).

Application Procedure

Patients presenting to the Atatürk University Faculty of Medicine Infectious Diseases and Clinical Microbiology Clinic between June, 2008 and June, 2010 and meeting the inclusion criteria were enrolled. All subjects enrolled were administered a socio-demographic data questionnaire and the SF-36 before IFN therapy and on the 3rd and 6th months of treatment.

Statistical Analysis

All the study data were coded numerically and subjected to the One-Way Analysis of Variance and the Mann-Whitney U test in a computer environment using the Statistical Package for Social Sciences (SPSS) v.18.0. A p value of less than 0.05 was considered statistically significant.

Results

Socio-demographic Characteristics

Socio-demographic characteristics of the patients are presented in Table 1.

Quality of Life Scores

Physical functioning, social functioning, physical role limitations, emotional role limitations, mental health, energy/vitality, bodily pain and general health perception scores based on responses to the questions in the SF-36 were obtained for the patient group consisting of patients with HBV and HCV and receiving PEG-IFN

therapy and for the control group consisting of healthy adults. Physical functioning (p=0.007), physical role limitations (p=0.008), emotional role limitations (p=0.007), vitality/energy (p=0.001), and general health (p=0.001) scores before treatment in the patient group were statistically significantly lower than in the control group. On the 3rd month of treatment, a statistically significant decrease was observed in the physical role limitations (p=0.03), emotional role limitations (p=0.01) and vitality/energy (p=0.002) scores in the patient group. On the 6th month of treatment, a statistically significant decrease was determined in the physical functioning (p=0.001), physical role limitations (p=0.004), emotional role limitations (p=0.004), mental health (p=0.004) and vitality/energy (p=0.0003) scores. When quality of life scores of patients with CHB and CHC were compared with pre-treatment values, a statistically significant decrease was determined in the emotional role limitations scores (p=0.027) in patients with CHC. A statistically significant decrease was also observed in the physical functioning (p=0.042) and social functioning (p=0.042) scores in patients with CHC on the 6th month of treatment. When we compared the pre-treatment HRQoL scores of patients with CHB and controls, we determined statistically significantly lower vitality/energy (p=0.01) and general health (p=0.01) scores in the patient group than in controls. On the 6th month of treatment, statistically significant differences were determined in the physical functioning (p=0.03), physical role limitations (p=0.011), emotional role limitations (p=0.003) and vitality/energy (p=0.006) scores in patients with CHB. When we compared the pre-treatment HRQoL scores of patients with CHC and controls, we determined statistically significantly lower physical functioning (p=0.006), physical role limitations (p=0.006), emotional role limitations (p=0.001), vitality/energy (p=0.000005), and general health (p=0.003) scores in patients with chronic hepatitis. A statistically significant decrease was determined in physical functioning (p=0.006), physical role limitations (p=0.013), emotional role limitations (p=0.001), mental health (p=0.041) and vitality/energy (p=0.000005) scores in patients with hepatitis C on the 3rd month of treatment. On the 6th month of treatment, statistically significant decreases were observed in physical functioning (p=0.000008), social functioning (p=0.005), physical role

Table 1. Socio-demographic characteristics of the groups

		Groups								p			
		Patient (all)		CHB		CHC		Control					
		Number	%	Number	%	Number	%	Number	%	Patient-control	CHB-CHC	CHB-control	CHC-control
Gender	Female	24	47.1	8	28.6	16	69.6	24	47.1	1	0.778	0.108	0.068
	Male	27	52.9	20	71.4	7	30.4	27	52.9				
Marriage status	Married	37	72.5	20	71.4	17	73.9	42	82.4	0.348	0.691	0.574	0.321
	Single	12	23.5	8	28.6	4	17.4	7	13.7				
	Widowed	2	3.9	0	0	2	8.7	2	3.9				
Place of residence	Province/city	26	51	13	46.4	13	56.5	17	33.3	0.901	0.644	0.858	0.675
	District	9	17.6	6	21.4	3	13	26	51				
	Town/village	16	31.4	9	32.2	7	30.5	8	15.7				
Educational status	Illiterate	9	17.6	2	7.1	7	30.4	6	11.8	0.862	0.082	0.413	0.216
	Literate	5	9.8	2	7.1	3	13	10	19.6				
	Elementary school	22	43.2	15	53.7	7	30.4	19	37.3				
	High school	11	21.6	7	25	4	17.5	12	23.5				
	University	4	7.8	2	7.1	2	8.7	4	7.8				
Occupations	Unemployed	2	3.9	2	7.1	0	0	2	3.9	0.507	0.247	0.237	0.848
	Seasonal agricultural worker	1	2	0	0	1	4.3	2	3.9				
	Employee	6	11.8	3	10.7	3	13	8	15.7				
	Housewife	20	39.2	7	25	13	56.5	18	35.3				
	Worker	2	3.9	2	7.1	0	0	7	13.7				
	Self-employment	10	19.6	8	28.6	2	8.7	6	11.8				
	Student	5	9.8	2	7.1	3	13	2	3.9				
	Other	5	9.8	4	14.3	1	4.3	6	11.8				

CHB: Chronic hepatitis B, CHC: Chronic hepatitis C

limitations (p=0.0000008), emotional role limitations (p=0.000007), mental health (p=0.001) and vitality/energy (p=0.000005) scores. Mean values, standard deviation and p values obtained for all groups in the study before and after 3 and 6 months of treatment are shown in Table 2. Distribution of SF-36 scores by socio-demographic properties of patients is summarized in Table 3. Distribution of SF-36 scores by socio-demographic properties of CHB patients in treatment periods is summarized in Table 4. Distribution of SF-36 scores by socio-demographic properties of CHC patients in treatment periods is summarized in Table 5.

Discussion

Patients with chronic hepatitis are generally asymptomatic, but may also exhibit systemic symptoms, such as fatigue, nausea, pruritus, lack of appetite and psychological disorders. A significant impairment in HRQoL may occur in this patient group. The majority of studies of HRQoL in chronic viral hepatitis have been concerned with HCV infection, while the number of studies concerning HBV infection is limited (4). HRQoL of patients with chronic hepatitis may vary depending on their socio-demographic characteristics. Numerous studies have shown that sex, marital status, education level, occupation and place of residence affect HRQoL of HBV- and HCV-infected patients. In agreement with the previous literature, we determined a significant decrease in female patients with chronic hepatitis (11,12,13,14,15,16,17,18, 19,20). Women with chronic disease are known to receive less social support than men in many parts of the world. In addition, they generally receive medical care later than males; they either have to work, or else have to resume their responsibilities without being fully recovered (21). These may all account for the decrease in HRQoL of female patients with chronic hepatitis. In agreement with previous studies, we determined lower HRQoL scores in individuals infected with HCV (22,23). Being married and having social and individual responsibilities may affect HRQoL. No significant change in HRQoL and only a weak correlation between marital status and HRQoL was observed in married patients

Table 2. Evaluation of short form-36 scores of patients in treatment periods

Before treatment								
	Physical functioning		**Social functioning**		**Physical role**		**Emotional role**	
		p		**p**		**p**		**p**
	Avg. ± SD	**Median; IQR**	**Avg. ± SD**	**Median; IQR**	**Avg. ± SD**	**Median; IQR**	**Avg. ± SD**	**Median; IQR**
Patient	63.1±34	0.007	81.3±25.5	0.472	43.6±46.1	0.008	36.8±34.8	0.007
Control	81.8±23.3	70;60	85±17.8	100;33.33	67.2±42	25;100	55±29.2	25;75
CHB	68.8±34	0.197	82.1±26.4	0.789	52.7±46.8	0.123	46.4±33.8	0.027
CHC	56.3±33.5	90;30	80.2±24.8	88.9;22.2	32.6±43.6	100;75	25±32.9	75;25
CHB	68.8±34	0.05	82.1±26.4	0.613	52.7±46.8	0.168	46.4±33.8	0.28
Control	81.8±23.3	82.5;48.75	85±17.8	100;30.56	67.2±42	62.5;100	55±29.2	25;25
CHC	56.3±33.5	0.006	80.2±24.8	0.451	32.6±43.6	0.006	25±32.9	0.001
Control	81.8±23.3	60;60	85±17.8	100;77.78	67.2±42	0;100	55±29.2	0;75
3rd months of treatment								
Patient	69.1±45.3	0.06	78±30	0.177	48±47.1	0.03	38.2±36.9	0.01
Control	81.8±23.3	80;55	85±17.8	100;44.44	67.2±42	25;100	55±29.2	25;75
CHB	78±30	0.122	80.2±29.5	0.575	52.7±46.3	0.444	44.6±36.2	0.173
CHC	58.3±57.8	90;30	75.4±31.1	88.9;22.22	42.4±48.5	100;75	30.4±36.9	75;25
CHB	78±30	0.573	80.2±29.5	0.389	52.7±46.3	0.168	44.6±36.2	0.192
Control	81.8±23.3	95;41.25	85±17.8	100;41.67	67.2±42	62.5;100	55±29.2	75;75
CHC	58.3±57.8	0.006	75.4±31.1	0.097	42.4±48.5	0.013	30.4±36.9	0.001
Control	81.8±23.3	65;90	85±17.8	100;44.44	67.2±42	0;100	55±29.2	0;75
6th months of treatment								
Patient	59.2±31.6	0.001	76.7±28.8	0.109	31.9±42.4	0.004	23.5±32.9	0.004
Control	81.8±23.3	60;55	85±17.8	88.88;44.44	67.2±42	0;75	55±29.2	0;75
CHB	67.3±27.4	0.042	83.7±23.7	0.042	40.2±44.3	0.124	31.3±36.4	0.064
CHC	49.3±34.1	90;30	68.1±32.5	88.9;22.2	21.7±38.7	100;75	14.1±25.9	75;25
CHB	67.3±27.4	0.03	83.7±23.7	0.824	40.2±44.3	0.011	31.3±36.4	0.003
Control	81.8±23.3	75;52.5	85±17.8	100;30.56	67.2±42	25;100	55±29.2	0;75
CHC	49.3±34.1	0.000008	68.1±32.5	0.005	21.7±38.7	0.0000008	14.1±25.9	0.000007
Control	81.8±23.3	55;55	85±17.8	77.77;55.56	67.2±42	0;25	55±29.2	0;25

with chronic viral hepatitis B in previous studies. In the present study also, no significant changes in HRQoL were determined in this patient group. A low education level is another demographic characteristic that affects HRQoL. As also shown in several studies, HRQoL was statistically significantly affected before and during treatment in our chronic hepatitis patients with a low level of education (13,16). Housewives have been determined to have the lowest scores and clerical workers the highest in all areas of HRQoL (17). Low physical functioning, physical role limitations, general health and emotional role limitations scores have been determined among unemployed patients with CHB and CHC (13). In our study, pre-treatment physical functioning and 3rd month physical role limitations scores in patients with CHB were lower among housewives. Among the patients with CHC, a significant decrease was observed only in the mental health scores in agricultural workers at the 6th month of treatment. The effect of IFN therapy in terms of occupations of patients with chronic viral hepatitis is unclear, and no benchmark has been determined. However, the numerous side-effects of IFN and ribavirin may be described as an adverse physical impact. Lam et al. (11) showed a significant level of variation in HRQol scores in patients with CHB in the categories of physical role limitations, bodily pain, energy/vitality, social functioning and emotional role limitations. In a similar study of patients with hepatitis B and C and healthy controls, Ozkan et al. (13) observed a particularly significant decrease in the physical functioning and mental health domains in patients with HBV infection compared to controls. Several studies have reported lower HRQoL scores in patients with HBV and HCV infection compared to healthy controls (11,12,13,24,25). In the present study, we determined lower HRQoL scores in patients with HBV infection compared to healthy controls. Patients with CHC have more severe and more frequent symptoms of musculoskeletal pain, malaise and fatigue compared with other forms of chronic liver disease (14,26). Several studies have shown a decrease in HRQoL scores in all categories in patients with hepatitis C compared to controls (12,13,22,24). In this

Table 2. Continued

Before treatment								
	Mental health		**Energy**		**Bodily pain**		**General health**	
		p		**p**		**p**		**p**
	Avg .± SD	**Median; IQR**	**Avg. ± SD**	**Median; IQR**	**Avg. ± SD**	**Median; IQR**	**Avg. ± SD**	**Median; IQR**
Patient	59.8±23.3	0.37	39.1±29.8	0.001	59.5±31.8	0.446	45.5±21	0.001
Control	63.8±21.5	60;40	57.9±22.4	30;60	63.8±20.5	55.55;55.55	59.9±18.8	46;27.5
CHB	62.9±24.2	0.3	41.6±33.9	0.516	66.3±33.5	0.093	47.1±22.3	0.562
CHC	56±21.9	64;28	36.1±24.2	60;30	54.2±28.2	66.7;33.4	43.6±19.6	57.5;20
CHB	62.9±24.2	0.865	41.6±33.9	0.01	66.3±33.5	0.712	47.1±22.3	0.01
Control	63.8±21.5	68;36	57.9±22.4	30;63.75	63.8±20.5	77.77;66.67	59.9±18.8	47.25;19.75
CHC	56±21.9	0.284	36.1±24.2	0.000005	54.2±28.2	0.132	43.6±19.6	0.003
Control	63.8±21.5	60;44	57.9±22.4	30;40	63.8±20.5	44.44;44.44	59.9±18.8	45;32.5
3rd months of treatment								
Patient	56.9±24.4	0.127	41±30	0.002	61±29	0.621	54.8±24	0.242
Control	63.8±21.5	64;28	57.9±22.4	45;50	63.8±20.5	66.66;44.44	59.9±18.8	53.5;35
CHB	60.7±25	0.227	45.9±29.9	0.2	65.9±29.8	0.189	56.2±23.8	0.642
CHC	52.3±23.4	64;28	35±29.7	60;30	55.1±27.5	66.7;33.4	53±24.5	57.5;20
CHB	60.7±25	0.569	45.9±29.9	0.06	65.9±29.8	0.758	56.2±23.8	0.476
Control	63.8±21.5	64;24	57.9±22.4	50;50	63.8±20.5	72.22;55.56	59.9±18.8	54.75;35
CHC	52.3±23.4	0.041	35±29.7	0.000005	55.1±27.5	0.229	53±24.5	0.149
Control	63.8±21.5	52;40	57.9±22.4	40;60	63.8±20.5	44.44;55.56	59.9±18.8	53.5;35
6th months of treatment								
Patient	50.9±20.6	0.004	35.6±28	0.0003	52.7±32.5	0.05	56.5±24.8	0.439
Control	63.8±21.5	52;32	57.9±22.4	40;100	63.8±20.5	55.55;55.56	59.9±18.8	62.5;41
CHB	56±20.9	0.05	39.5±28.4	0.279	54.4±32.1	0.695	57.2±26	0.833
CHC	44.7±18.8	64;28	30.9±27.3	60;30	50.7±33.6	66.7;33.4	55.7±23.9	57.5;20
CHB	56±20.9	0.149	39.5±28.4	0.006	54.4±32.1	0.153	57.2±26	0.6
Control	63.8±21.5	60;23	57.9±22.4	45;50	63.8±20.5	50;61.11	59.9±18.8	66;41.88
CHC	44.7±18.8	0.001	30.9±27.3	0.000005	50.7±33.6	0.063	55.7±23.9	0.352
Control	63.8±21.5	48;32	57.9±22.4	30;50	63.8±20.5	55.55;55.56	59.9±18.8	60;40

CHB: Chronic hepatitis B, CHC: Chronic hepatitis C, IQR: Interquartile range, SD: Standard deviation, IQR: Interquartile range, Avg.: Average

Table 3. Distribution of short form-36 scores by socio-demographic properties of patients

Before treatment		Physical functioning		Social functioning		Physical role		Emotional role	
		Avg. ± SD M; IQR	p	Avg. ± SD M; IQR	p	Avg. ± SD M; IQR	p	Avg. ± SD M; IQR	p
Gender	Male	82.7±23.3 (95;26.25)	0.0003	87.7±18.4 (100;22.22)	0.03	64.8±42.5 (100;81.25)	0.03	52.8±29.4 (75;50)	0.02
	Female	82.7±33.7 (65;60)		78±24.5 (77.8;44.4)		44.8±46.7 (25;100)		38±35.7 (25;75)	
Marriage status	Married	56.6±35.4 (80;55)	0.298	80.8±25.9 (89.9;33.3)		36.5±44.3 (50;100)	0.46	33.8±35 (75;75)	0.99
	Single	82.5±24.3 (95;20)		81.5±26.9 (100;22.2)		64.6±45.8 (100;100)		43.8±35.6 (75;75)	
	Widow/widower	67.5±10.6 (75;22.5)		88.9±15.7 (88.8;47.26)	0.92	50±70.7 (62.5;93.75)		50±35.4 (50;68.75)	
Education	Illiterate	47.3±21.7 (45;35)	0.003	79.3±21.4 (77.8;44)	0.91	30±39.2 (0;75)	0.01	28.3±35.2 (0;75)	0.02
	Literate	72.3±27.4 (80;40)		80.7±24.7 (88.9;33.3)		58.3±47.9 (100;100)		48.3±33.4 (75;75)	
	Elementary school	72.6±33.3 (85;42.5)		84.6±23 (100;22.22)		48.2±46.9 (25;100)		42.7±33.7 (50;75)	
	High school	85±23.3 (100;30)		85±21.6 (100;22.22)		78.3±34.8 (100;25)		63±23.7 (75;25)	
	University	83.1±30.5 (95;18.75)		81.9±15.6 (83.35;27.78)		68.8±45.8 (100;87.5)		40.6±35.2 (50;75)	
Place of residence	Province/city	66.3±32.7 (95;40)	0.426	85.5±25.3 (100;22.22)	0.39	51.9±46.3 (100;100)	0.1	46.2±34.4 (75;50)	0.72
	District	58.9±37.9 (75;50)		72.8±30.5 (77.8;33.3)		44.4±48.1 (50;100)		33.3±35.4 (50;75)	
	Town/village	60.3±35.7 (80;48.75)		79.2±22.9 (88.88;33.32)		29.7±44 (12.5;100)		23.4±32.2 (25;75)	
3rd month of treatment									
Gender	Male	84.1±26.2 (100;25)	0.01	84.6±23.6 (100;24.99)	0.18	67.6±42 (100;75)	0.02	55.6±29 (75;31.25)	0
	Female	65.7±43.6 (72.5;57.5)		78±25.9 (88.89;41.63)		46.4±47 (25;100)		36.5±36.8 (25;75)	
Marriage status	Married	68.2±48.4 (85;45)	0.118	79.9±29.6 (100;33)	0.46	44.6±49.3 (75;100)	0.29	35.8±37.1 (75;75)	0.22
	Single	83.3±23.9 (100;30)		75±29.6 (89.9;22.22)		66.7±35.9 (100;75)		52.1±34.5 (75;75)	
	Widow/widower	0±0 (36.5;86.25)		61.1±55 (72.22;72.23)		0±0 (12.5;81.25)		0±0 (0;56.25)	
Education	Illiterate	36±32.2 (35;70)	0.003	74.1±30.2 (77.8;44)	0.35	16.7±34.9 (0;0)	0.02	20±34.3 (0;75)	0.02
	Literate	74.7±30.3 (90;30)		84.4±22.1 (100;33.3)		58.3±47.9 (100;100)		46.7±35.2 (75;75)	
	Elementary school	83.7±38.6 (95;35)		85.4±21.3 (100;38.87)		63.4±44.1 (100;87.5)		51.8±31.8 (75;50)	
	High school	86.5±21.1 (100;20)		81.6±26.3 (88.9;22.22)		73.9±38 (100;50)		55.4±30.1 (75;50)	
	University	76.9±34 (90;33.75)		69.4±30.1 (77.78;52.79)		56.3±49.6 (75;100)		43.8±37.2 (62.5;75)	
Place of residence	Province/city	64±37.8 (95;35)	0.213	76.9±30.6 (88.9;22.22)	0.58	49±46.6 (100;100)	0.33	39.4±36.9 (75;75)	0.63
	District	59.4±45.7 (75;55)		67.9±34.4 (77.8;44.4)		30.6±46.4 (50;100)		25±37.5 (50;75)	
	Town/village	82.8±55.2 (85;28.75)		85.4±26.2 (100;30)		56.3±48.7 (100;100)		43.8±37.1 (75;75)	

Table 3. Continued

Before treatment		Mental health	p	Energy	p	Bodily pain	p	General health	p
		Avg. ± SD		Avg. ± SD		Avg. ± SD		Avg. ± SD	
		M; IQR		M; IQR		M; IQR		M; IQR	
Gender	Male	65.1±20.5	0.11	53.2±28.5	0.07	69.5±24.1	0	57.5±20.9	0.02
		(68;28)		(50;45)		(77.77;47.22)		(55.5;24.13)	
	Female	58±24		43.2±26.4		52.8±27		47.4±20.2	
		(60;40)		(40;43.75)		(55.57;44.44)		(48.5;33)	
Marriage status	Married	56.1±22.5	0.57	30.9±26.7	0.08	55±31.7	0.03	43.9±21.1	0.88
		(60;36)		(50;50)		(55.6;33.4)		(52.5;26)	
	Single	69.7±25.3		59.2±29.1		74.1±30.1		50±22.2	
		(72;44)		(70;50)		(78.8;44.44)		(48.5;22.5)	
	Widow/widower	68±0		70±14.1		55.6±31.4		48.8±15.9	
		(68;6)		(67.5;18.75)		(38.86;44.45)		(55;22)	
Education	Illiterate	49.6±19.2	0.25	38.7±24.4	0.48	43.7±23.9	0.56	43.4±20.2	0.38
		(52;28)		(40;45)		(44.44;44.5)		(38.8;45)	
	Literate	65.1±22.1		53.3±28.2		63±20.4		54.8±15.9	
		(68;36)		(55;55)		(77.77;33.4)		(52.5;17.5)	
	Elementary school	64.5±22.3		46.6±30.4		62.9±27.8		52.6±22.1	
		(68;38)		(40;55)		(55.6;38.92)		(53.5;24.75)	
	High school	63±22.1		53.3±27.3		69.6±27.1		55.3±24.5	
		(38;28)		(50;30)		(66.7;44.44)		(56;21)	
	University	61±26.8		54.4±20.1		63.9±25.7		59.4±12.3	
		(72;43)		(57.5;36.25)		(55.57;50.04)		(48.8;17)	
Place of residence	Province/city	60.3±24.1	0.36	42.7±29.5	0.44	65.4±32.3	0.1	49.4±21.3	0.09
		(68;40)		(50;40)		(77.77;44.44)		(53.5;28.5)	
	District	56.4±22.8		39.4±39.1		65.4±32.1		44.2±28	
		(60;28)		(50;45)		(55.6;33.4)		(55;26)	
	Town/village	60.8±23.4		33.1±25		46.5±28.8		39.8±15.2	
		(66;35)		(47.5;55)		(50;44.47)		(46.75;15.5)	
3rd month of treatment									
Gender	Male	60.2±24.4	0.95	52.5±27.6	0.24	69.8±22.3	0	60.1±22.3	0.17
		(66;32)		(52.5;32.5)		(77.77;36.11)		(60;31)	
	Female	60.5±21.9		46±27.7		54.2±25.6		54.2±20.4	
		(64;26)		(50;38.75)		(55.6;55.56)		(52.25;24.38)	
Marriage status	Married	54.7±24.3	0.75	38.6±29.9	0.7	59.5±29.4	0.01	55.5±24.2	0.71
		(64;24)		(50;40)		(55.6;33.36)		(57.5;28.5)	
	Single	61.7±26.6		52.5±29		70.4±26.9		55±24.6	
		(64;48)		(55;50)		(77.77;22.22)		(51;16)	
	Widow/widower	70±2.8		15±21.2		33.3±15.7		40.5±18.4	
		(70;7)		(43;63.75)		(32.33;22.21)		(51.75;27.88)	
Education	Illiterate	54.1±21.4	0.36	32±24.8	0.03	43.7±24.7	0.01	46.4±20.2	0.33
		(56;24)		(30;50)		(44.44;44.48)		(42.5;27.5)	
	Literate	66.9±22		55.7±28.5		60.7±23		60.7±15.6	
		(72;28)		(60;35)		(66.66;33.4)		(57.5;22.5)	
	Elementary school	63±22.4		52.9±27.3		66.4±25.3		58.9±22.4	
		(64;30)		(60;45)		(66.66;44.46)		(60;28.5)	
	High school	58.8±25.1		55.2±26.9		69.6±21		59.1±24	
		(68;32)		(60;30)		(66.7;33.29)		(56;16)	
	University	50.5±26		36.3±23.7		59.7±26.5		58.4±20.3	
		(58;49)		(45;43.75)		(50;41.71)		(49.25;42.63)	
Place of residence	Province/city	58.6±25.8	0.26	37.9±31.1	0.49	61.5±26.5	0.54	54.9±23.8	0.67
		(72;32)		(50;45)		(66.66;33.36)		(53.5;21)	
	District	47.6±23.9		37.8±29.9		63±36.9		46.4±25.3	
		(52;32)		(50;40)		(55.6;33.4)		(56;26)	
	Town/village	59.5±22.7		47.8±29		59±30		59.2±23.6	
		(66;30)		(60;37.5)		(77.77;41.7)		(58.75;30.13)	

Table 3. Continued

Before treatment		Physical functioning	p	Social functioning	p	Physical role	p	Emotional role	p
		Avg. ± SD		Avg. ± SD		Avg. ± SD		Avg. ± SD	
		M; IQR		M; IQR		M; IQR		M; IQR	
6th Month of treatment									
Gender	Male	78.2±29	0.005	83.1±23.7	0.31	57.4±44.1	0.06	44.9±33.1	0.08
		(90;30)		(100;24.99)		(75;100)		(50;75)	
	Female	61.8±28.7		78.2±24.7		40.6±46		32.8±35.8	
		(62.5;52.5)		(83.34;33.33)		(12.5;100)		(12.5;75)	
Marriage status	Married	54.5±33.3	0.441	75.1±30.4	0.19	31.1±43.1	0.72	23±33	0.44
		(75;55)		(88.9;33.33)		(50;100)		(50;75)	
	Single	76.3±21.4		85.2±22.4		39.6±43.2		29.2±35.1	
		(90;40)		(88.9;22.2)		(50;100)		(25;75)	
	Widow/widower	45±14.1		55.6±31.4		0±0		0±0	
		(65;46.25)		(61.08;58.34)		(12.5;81.25)		(0;56.25)	
Education	Illiterate	42.3±23.1	0.01	69.6±27.4	0.3	15±28	0.02	16.7±30.9	0.53
		(40;30)		(77.77;44.44)		(0;25)		(0;25)	
	Literate	69.7±32		81.5±28.4		53.3±47.1		43.3±34.7	
		(85;60)		(100;33.3)		(50;100)		(50;75)	
	Elementary school	72.8±29.4		83.5±24.6		52.4±46		43.9±34.8	
		(80;47.5)		(100;38.87)		(50;100)		(75;75)	
	High school	82.2±23.9		85±16.3		64.1±42.5		46.7±33.1	
		(90;30)		(88.88;22.22)		(75;100)		(75;75)	
	University	79.4±27.4		75±25		50±53.5		28.1±33.9	
		(92.5;41.25)		(83.34;27.79)		(50;100)		(12.5;68.75)	
Place of residence	Province/city	56.9±31.7	0.881	78.6±25.7	0.85	32.7±42.9	0.69	22.1±31.1	0.77
		(80;40)		(88.9;22.22)		(75;100)		(25;75)	
	District	57.2±32.5		70.4±32.9		22.2±38.4		25±37.5	
		(70;55)		(88.8;44.4)		(50;100)		(50;75)	
	Town/village	64.1±32.4		77.1±32.6		35.9±45.6		25±22.1	
		(80;47.5)		(100;33.2)		(25;100)		(25;75)	

Table 3. Continued

Before treatment		Mental health	p	Energy	p	Bodily pain	p	General health	p
		Avg. ± SD		Avg. ± SD		Avg. ± SD		Avg. ± SD	
		M; IQR		M; IQR		M; IQR		M; IQR	
6th Month of treatment									
Gender	Male	58.1±22.5	0.72	49.2±26.9	0.35	64.2±26.8	0.02	61.2±23.1	0.14
		(60;28)		(56;36.25)		(66.66;36.17)		(61;32.5)	
	Female	56.5±21.4		44.1±28.4		51.6±27.2		54.8±20.3	
		(56;26)		(47.5;42.5)		(55.57;41.7)		(59.25;23.25)	
Marriage status	Married	48.4±20.8	0.93	34.7±29.8	0.97	52±33.8	0.04	55.4±24.4	0.85
		(56;24)		(50;40)		(55.6;33.4)		(61;27.5)	
	Single	58.3±20.7		40±22.3		60.2±28.2		58.3±28.5	
		(64;40)		(45;45)		(66.7;44.49)		(57.5;31)	
	Widow/widower	52±5.7		25±35.4		22.2±15.7		67.3±12.4	
		(60;20)		(55;58.75)		(27.76;27.75)		(61;20.75)	
Education	Illiterate	46.9±17.1	0.26	28.7±24.5	0.06	44.4±29.7	0.22	50.7±22.9	0.56
		(48;16)		(30;50)		(44.44;44.45)		(62.5;34)	
	Literate	61.9±27.3		52.3±30.3		56.3±22.8		56.6±13.7	
		(68;28)		(55;35)		(66.66;44.67)		(52.5;17.5)	
	Elementary school	58.7±22.3		49.1±28		60.7±28.1		58.6±23.5	
		(60;28)		(50;40)		(55.6;38.94)		(61;31.75)	
	High school	60.7±18.1		52.8±25.8		65.2±25.1		63.1±23.1	
		(64;24)		(50;30)		(66.7;33.36)		(61;21.75)	
	University	51.5±25		40.6±20.6		55.6±32.5		59.4±22.6	
		(58;45)		(37.5;35)		(50;63.90)		(56.25;40.13)	
Place of residence	Province/city	54.6±25	0.44	33.8±28.9	0.54	50.9±31.5	0.55	56.9±23.4	0.51
		(64;24)		(50;45)		(55.6;33.4)		(62.5;21.75)	
	District	39.6±23.5		35.6±21.9		45.7±37.5		46.3±22.8	
		(52;36)		(50;40)		(55.6;33.4)		(57.5;26)	
	Town/village	51.3±22.2		38.4±30.8		59.7±32.2		61.7±27.9	
		(62;28)		(50;47.5)		(61.13;55.56)		(62.5;33.88)	

Avg: Average, M: Median, IQR: Interquartil range, SD: Standard deviation

Table 4. Distribution of short form-36 scores by sociodemographic properties of chronic hepatitis B patients in treatment periods

		Physical functioning		Social functioning		Physical role		Emotional role	
Before treatment		**Avg. ± SD**	**p**	**Avg. ± SD**	**p**	**Avg. ± SD**	**p**	**Avg. ± SD**	**p**
Gender	Male	85.3±16.4	0.00009	88.9±15.3	0.03	68.8±41.3	0.002	56.3±29.1	0.012
	Female	27.5±31.7		65.3±40		12.5±35.4		21.9±33.9	
Marriage status	Married	63.5±35.3	0.202	86.1±24.9	0.215	50±48	0.641	48.8±32.9	0.576
	Single	81.9±28		72.2±29.1		59.4±46.2		40.6±37.6	
Education	Illiterate	17.5±3.5	0.234	77.8±31.4	0.946	50±70.7	0.393	37.5±53	0.389
	Literate	62.5±10.6		94.4±7.9		0±0		12.5±17.7	
	Elementary school	72±36.3		81.5±27.4		48.3±50.4		45±35.6	
	High school	72.1±31.9		84.1±33.2		71.4±36.6		64.3±19.7	
	University	90±7.1		72.2±7.9		75±35.4		37.5±53	
Occupation	Unemployed	97.5±3.5	0.005	77.8±31.4	0.196	100±0	0.113	75±0	0.071
	Employee	88.3±16.1		92.5±12.8		83.3±28.9		75±0	
	Housewife	29.3±33.8		73±36.2		14.3±37.8		21.4±36.5	
	Worker	90±14.1		88.9±15.7		62.5±53		37.5±53	
	Self-employment	78.8±21.2		90.2±16.2		56.2±47.7		53.1±28.1	
	Student	50±49.5		38.9±39.3		25±35.4		12.5±17.7	
	Other	87.5±13.2		94.4±6.4		75±50		62.5±25	
Place of residence	Province/city	74.6±29.1	0.656	66.7±34.3	0.259	77.8±18.4	0.449	36.1±48.6	0.183
	District	59.2±46.1		68.8±34		82.1±26.4		52.7±46.8	
	Town/village	74.6±29.1		90.6±25.6		59.6±45.1		57.7±29.6	
3rd month of treatment									
Gender	Male	90.5±14.4	0.0005	81.7±29.6	0.677	71.3±41.6	0.00005	58.8±29.6	0.00006
	Female	46.9±36.8		76.4±31.1		6.3±11.6		9.4±26.5	
Marriage status	Married	75.5±31	0.49	83.9±26.9	0.299	47.5±49.3	0.359	40±36.6	0.292
	Single	84.4±28.2		70.8±35.6		65.6±37.6		56.3±34.7	
Education	Illiterate	27.5±38.9	0.15	94.4±7.9	0.52	0±0	0.101	0±0	0.085
	Literate	85±21.2		94.4±7.9		0±0		0±0	
	Elementary school	85±27.7		83±23		66.7±43		56.7±32	
	High school	75.7±30.5		74.6±43.9		60.7±49.7		46.4±36.6	
	University	77.5±10.6		50±39.3		25±35.4		37.5±53	
Occupation	Unemployed	100±0	0.051	77.8±31.4	0.881	87.5±17.7	0.025	75±0	0.105
	Employee	81.7±12.6		74.1±44.9		66.7±57.7		75±0	
	Housewife	50.7±38		84.1±23.9		3.6±9.4		21.4±36.6	
	Worker	100±0		88.9±15.7		100±0		75±0	
	Self-employment	88.8±18.1		83.3±35.6		65.6±48.1		50±43.3	
	Student	52.5±46		50±39.3		37.5±17.7		10.7±28.3	
	Other	92.5±15		83.3±26.4		68.8±47.3		75±0	
Place of residence	Province/city	83.1±51.6	0.72	80.3±33.7	0.974	61.5±45.2	0.657	53.8±33.6	0.473
	District	72.5±47.1		77.8±27.2		45.8±51		37.5±41.1	
	Town/village	74.4±33.2		81.5±27.8		44.4±48.1		36.1±37.7	

Table 4. Continued

		Mental health		Energy		Bodily pain		General health	
Before treatment		**Avg. ±SD**	**p**	**Avg. ±SD**	**p**	**Avg. ±SD**	**p**	**Avg. ±SD**	**p**
Gender	Male	67.8±20.4	0.088	51.3±33.9	0.014	76.1±27	0.011	53±21	0.023
	Female	50.5±29.9		17.5±19.8		41.7±37		32.3±19.1	
Marriage status	Married	60.8±21.9	0.488	34±31.8	0.059	65±34.1	0.757	47.6±22.1	0.842
	Single	68±30.4		60.6±33.4		69.4±34		45.7±24.4	
Education	Illiterate	48±5.65	0.282	35±35.4	0.531	16.7±7.9	0.272	18.8±1.76	0.222
	Literate	40±11.3		20±0		55.6±31.4		43±11.3	
	Elementary school	69.9±20.7		44.7±35.3		70.4±32.7		54.7±21.8	
	High school	54.9±33.3		33.6±37.7		71.4±35.1		40.1±25.1	
	University	76±5.7		75±7.1		77.8±31.4		46.8±2.5	
Occupation	Unemployed	72±17	0.234	45±49.5	0.611	83.3±23.6	0.234	41±14.1	0.232
	Employee	74.7±6.1		83.3±15.3		92.6±12.8		35.8±17.6	
	Housewife	56.6±26.4		20±20		44.4±39		46.8±13.1	
	Worker	84±22.6		62.5±17.7		55.6±15.7		49.1±22.1	
	Self-employment	61.5±24.7		28.8±30.6		73.6±32.5		28±29	
	Student	40±45.3		35±49.5		38.9±23.6		70.1±28.8	
	Other	64±23.8		65±34.2		80.6±31.9		41±14.1	
Place of residence	Province/city	30.6±34.9	0.393	68.9±20.5	0.649	32.8±29.7	0.237	50.6±33.4	0.602
	District	46.4±33.8		62.9±24.2		42.6±33.9		66.3±33.5	
	Town/village	64±25.5		46.5±32.4		72.6±31.6		51.6±50.6	
3rd month of treatment									
Gender	Male	63±26.6	0.455	51.5±30.7	0.118	72.2±24.6	0.074	59.5±22.9	0.26
	Female	55±21		31.9±23.9		50±37.1		48.1±25.5	
Marriage status	Married	61.6±22.8	0.773	44.5±29.1	0.704	65±30.2	0.811	56.3±21.5	0.972
	Single	58.5±31.6		49.4±33.5		68.1±30.5		55.9±30.4	
Education	Illiterate	60±5.7	0.462	40±14.1	0.604	33.3±15.7	0.479	41.3±1.8	0.603
	Literate	64±17		35±21.2		72.2±39.3		62.5±17.7	
	Elementary school	68±19.8		54.7±27.7		71.9±30.5		62.2±22.8	
	High school	49.7±36		36.4±38.4		65.1±26.8		47.7±27	
	University	42±31.1		30±35.4		50±39.3		49.8±40.7	
Occupation	Unemployed	72±11.3	0.862	75±7.1	0.73	88.9±15.7	0.716	46±21.2	0.974
	Employee	53.3±28.9		45±35		59.3±39		57.7±38.9	
	Housewife	60.6±15		35.7±23		54±38.2		53.5±21.9	
	Worker	76±33.9		50±28.3		77.8±31.4		58±2.8	
	Self-employment	60.5±34		45±38.5		68.1±22.6		61.3±26.1	
	Student	40±33.9		30±35.4		50±39.3		44.3±48.4	
	Other	64±22.9		57.5±28.7		77.8±27.2		59.9±17.9	
Place of residence	Province/city	64.6±27.4	0.425	46.9±29.1	0.987	70.9±25.5	0.467	62±23.5	0.474
	District	48.7±25		45±32.7		70.4±34.2		48.4±27.2	
	Town/village	63.1±21.5		45±32.8		55.6±33.3		53.1±22.6	

Table 4. Continued

Before treatment									
		Physical functioning		Social functioning		Physical role		Emotional role	
		Avg. ± SD	p	Avg. ± SD	p	Avg. ± SD	p	Avg. ± SD	p
6th month of treatment									
Gender	Male	75.3±28.1	0.112	80.6±26	0.271	48.8±44.8	0.106	36.3±36.7	0.258
	Female	47.5±11		91.7±15.4		18.8±37.2		18.8±34.7	
Marriage status	Married	61.3±26.8	0.062	84.4±82.5	0.806	40±81.9	0.974	28.8±40.6	0.575
	Single	82.5±61.3		81.9±84.4		40.6±40		37.5±28.8	
Education	Illiterate	37.5±37.5	0.325	83.3±83.3	0.369	25±25	0.371	0±0	0.152
	Literate	42.5±42.5		88.9±88.9		0±0		0±0	
	Elementary school	73±73		86.7±86.7		50±50		45±45	
	High school	69.3±69.3		85.7±85.7		46.4±46.4		28.6±28.6	
	University	72.5±72.5		50±50		0±0		0±0	
Occupation	Unemployed	90±14.1	0.539	100±0	0.624	100±0	0.216	75±0	0.215
	Employee	76.7±22.5		74.1±44.9		58.3±52		33.3±38.2	
	Housewife	49.3±10.6		95.2±12.6		21.4±39.3		21.4±36.6	
	Worker	65±35.4		66.7±47.1		12.5±17.7		0±0	
	Self-employment	73.1±33.4		81.9±24.4		46.9±47.1		31.3±37.2	
	Student	62.5±38.9		72.2±7.9		0±0		0±0	
	Other	72.5±35.7		80.6±19		50±45.6		56.3±37.5	
Place of residence	Province/city	72.3±24.6	0.492	87.2±16.3	0.731	44.2±45.8	0.886	32.7±35.9	0.806
	District	55.8±33.4		77.8±30.6		33.3±43.8		37.5±41.1	
	Town/village	67.8±28.1		82.7±29.5		38.9±47		25±37.5	

Table 4. Continued

Before treatment									
		Mental health		Energy		Bodily pain		General health	
		Avg. ± SD	p	Avg. ± SD	p	Avg. ± SD	p	Avg. ± SD	p
6th month of treatment									
Gender	Male	57.2±22.7	0.64	44.8±27.3	0.121	58.3±33	0.309	62.1±25.1	0.113
	Female	53±16.7		26.3±28.3		44.4±29.1		44.8±25.8	
Marriage status	Married	57±37.5	0.697	37.8±53.5	0.622	53.3±43.8	0.793	56.8±56.9	0.894
	Single	53.5±57		43.8±37.8		56.9±53.3		58.3±56.8	
Education	Illiterate	48±0	0.463	15±21.2	0.561	50±7.9	0.78	41.3±37.1	0.66
	Literate	36±39.6		20±28.3		27.8±7.9		45.5±18.4	
	Elementary school	62.1±18.9		45.7±24.6		58.5±35		62.9±24.6	
	High school	52.6±23		38.6±35.8		57.1±35.4		57.2±25.8	
	University	50±19.8		40±42.4		44.4±31.4		41.8±48.4	
Occupation	Unemployed	70±8.5	0.862	70±0	0.713	100±0	0.425	57.5±47.5	0.924
	Employee	61.3±22		40±30		55.6±29.4		60±47.5	
	Housewife	58.3±8		30±28.3		46±31.1		48.7±25.1	
	Worker	56±50.9		25±35.4		66.7±31.4		52.5±28.3	
	Self-employment	59±18.6		44.4±29.5		43.1±37.8		66.5±21.5	
	Student	40±33.9		35±49.5		50±23.6		46.8±41.4	
	Other	43±28.5		40±27.1		63.9±27.8		58.6±21.1	
Place of residence	Province/city	63.4±18.1	0.111	48.5±27.9	0.3	58.1±31.8	0.823	65±22.1	0.243
	District	42±16.3		33.3±26.6		48.1±34.2		43.5±23.7	
	Town/village	54.7±24.1		30.6±29.2		53.1±34.1		55.1±31	

Avg: Average, SD: Standard deviation

Table 5. Distribution of short form-36 scores by sociodemographic properties of chronic hepatitis C patients in treatment periods

		Physical functioning		Social functioning		Physical role		Emotional role	
Before treatment		**Avg. ± SD**	**p**	**Avg. ± SD**	**p**	**Avg. ± SD**	**p**	**Avg. ± SD**	**p**
Gender	Male	63.6±30.6	0.5	84.1±30	0.63	28.6±48.8	0.78	17.9±31.3	0.5
	Female	53.1±35.2		78.5±23.1		34.4±42.7		28.1±34	
Marriage status	Married	48.5±34.8	0.15	74.5±26.3	0.16	20.6±34.5	0.06	16.2±29.2	0.09
	Single	83.8±18		100±0		75±50		50±35.4	
	Widow/widower	67.5±10.6		88.9±15.7		50±70.7		50±35.4	
Education	Illiterate	44.3±17.4	0.67	77.8±25.7	0.53	28.6±36.6	0.27	17.9±27.8	0.53
	Literate	65±44.4		59.3±39		66.7±57.7		50±43.3	
	Elementary school	57.1±43.7		85.7±21		7.14±18.9		14.3±28.3	
	High school	75±26.8		91.7±16.7		50±57.7		37.5±43.3	
	University	45±49.5		77.8±31.4		50±70.7		25±35.4	
Occupation	Seassonal agricultural worker	15	0.23	22.2	0.07	0	0.45	0	0.57
	Employee	40±27.8		85.2±25.7		0±0		0±0	
	Housewife	52.7±35.2		76.9±23.3		34.6±41.5		28.8±33.6	
	Self-employment	97.5±3.5		100±0		50±70.7		37.5±53	
	Student	78.3±17.6		100±0		66.7±57.7		41.7±38.2	
	Other	45		66.7		0		0	
Place of residence	Province/city	58.1±35.1	0.93	80.3±24.9	0.98	44.2±48	0.33	34.6±36.1	0.28
	District	58.3±20.8		77.8±22.2		8.3±14.4		8.3±14.4	
	Town/village	52.1±38.5		81±29.12		21.4±39.3		14.3±28.3	
3rd month of treatment									
Gender	Male	59.3±44.9	0.96	81±27	0.58	42.9±53.5	0.98	32.1±40.1	0.89
	Female	57.8±63.9		72.9±33.2		42.2±48.1		29.7±36.8	
Marriage status	Married	59.7±63.2	0.27	75.2±32.8	0.73	41.2±50.7	0.27	30.9±38	0.41
	Single	81.3±14.9		83.3±11.1		68.8±37.5		43.8±37.5	
	Widow/widower	0±0		61.1±55		0±0		0±0	
Education	Illiterate	17.1±28.6	0.12	61.9±38.9	0.37	14.3±37.8	0.46	10.7±28.3	0.46
	Literate	61.7±53.5		77.8±38.5		66.7±57.7		50±43.3	
	Elementary school	94.3±77.1		87.3±21.7		57.1±53.5		42.9±40.1	
	High school	77.5±21		88.9±12.8		43.8±42.7		25±35.4	
	University	32.5±46		50±39.3		50±70.7		37.5±53	
Occupation	Seassonal agricultural worker	0	0.76	33.3	0.51	0	0.21	0	0.27
	Employee	33.3±57.3		59.3±39		0±0		0 ±0	
	Housewife	58.8±68.9		76.1±33.9		46.2±51.9		34.6±38.9	
	Self-employment	100±0		100±0		100±0		75±0	
	Student	75±10		77.8±0		58.3±38.2		33.3±38.2	
	Other	50		100		0		0	
Place of residence	Province/city	45±39.2	0.15	73.5±28.2	0.13	36.5±46.3	0.08	25±35.4	0.07
	District	33.3±57.7		48.1±44.9		0±0		0±0	
	Town/village	93.6±76.9		90.5±25.2		71.4±48.8		53.6±36.6	

Table 5. Continued

		Mental health		Energy		Bodily pain		General health	
Before treatment		**Avg. ± SD**	**p**	**Avg. ± SD**	**p**	**Avg. ± SD**	**p**	**Avg. ± SD**	**p**
Gender	Male	65.7±21.8	0.165	42.9±26.9	0.39	60.3±29.3	0.32	53±20.3	0.13
	Female	51.8±21.3		33.1±23.2		57.2±27.7		39.5±18.4	
Marriage status	Married	50.6±22.5	0.132	27.4±19.3	0.005	43.1±24.8	0.03	39.4±19.6	0.2
	Single	73±13.2		56.3±22.1		83.3±21.3		58.6±16.3	
	Widow/widower	68±0		70±14.1		55.6±31.4		48.8±15.9	
Education	Illiterate	45.7±19.6	0.496	30±28.1	0.38	42.9±20.7	0.53	39.6±20.9	0.74
	Literate	60±24		45±31.2		66.7±22.2		39.5±23.4	
	Elementary school	54.9±24.2		25.7±16.2		42.9±28.3		40.6±21.7	
	High school	71±10.5		51.3±20.2		66.7±42.6		54.9±18.2	
	University	60±39.6		50±28.3		55.6±31.4		51.3±8.8	
Occupation	Seassonal agricultural worker	36	0.346	10	0.3	66.7	0.21	12.5	0.08
	Employee	62.7±27.2		23.3±5.8		51.9±23.1		56.7±12.6	
	Housewife	50.5±21.5		32.7±25.8		43.6±26.2		36.9±18.2	
	Self-employment	50±19.8		65±21.2		72.2±39.3		66.8±4.6	
	Student	76±14.4		48.3±18.9		77.8±22.2		54.8±17.7	
	Other	80		50		11.1		42.5	
Place of residence	Province/city	56.6±23.1	0.572	38.8±27.2	0.82	58.1±32.4	0.42	47.2±19.3	0.58
	District	66.7±6.1		30±26.5		44.4±11.1		42.5±25.4	
	Town/village	50.3±24.2		33.6±19.7		41.3±22.9		37.3±19.4	
3rd month of treatment									
Gender	Male	41.7±26.2	0.15	36.4±27.2	0.88	73±27.1	0.04	55.1±28.6	0.8
	Female	57±21.2		34.4±31.6		47.2±24.5		52.1±23.4	
Marriage status	Married	46.6±24.1	0.14	31.8±30.3	0.16	52.9±27.9	0.18	54.5±27.8	0.76
	Single	68±13.9		58.8±19.3		75±21		53±7.2	
	Widow/widower	70±2.8		15±21.2		33.3±15.7		40.5±18.4	
Education	Illiterate	52±25	1	14.3±23	0.13	38.1±25.5	0.16	39.8±25.7	0.45
	Literate	53.3±30.6		46.7±41.6		44.4±22.2		56.2±33	
	Elementary school	50.3±24.5		41.4±27.3		60.3±26.3		61.6±24	
	High school	56±25.3		57.5±20.6		77.8±24		63.3±19.7	
	University	52±28.3		22.5±31.8		66.7±31.4		44.3±8.1	
Occupation	Seassonal agricultural worker	20	0.06	0	0.27	44.4	0.32	22.5	0.38
	Employee	25.3±8.3		13.3±23.1		63±32.1		41.2±30.1	
	Housewife	58.5±22		33.1±31.2		45.3±25.8		53.6±25.8	
	Self-employment	66±19.8		65±7.1		66.7±31.4		68.5±7.1	
	Student	64±13.9		55±21.8		70.4±23.1		49.5±1.8	
	Other	24		40		100		91	
Place of residence	Province/city	52.6±23.5	0.85	28.8±31.5	0.21	52.1±25	0.63	47.9±22.9	0.18
	District	45.3±26.6		23.3±20.8		48.1±44.9		42.5±26	
	Town/village	54.9±25.1		51.4±25.4		63.5±27		67.1±24.1	

Table 5. Continued

Before treatment									
		Physical functioning		Social functioning		Physical role		Emotional role	
		Avg. ± SD	p	Avg. ± SD	p	Avg. ± SD	p	Avg. ± SD	p
6th month of Treatment									
Gender	Male	57.9±40.8	0.44	73±35.6	0.64	28.6±48.8	0.59	14.3±28.3	0.99
	Female	45.6±31.5		66±32.1		18.8±34.8		14.1±25.8	
Marriage status	Married	46.5±39	0.67	64.1±34.8	0.28	20.6±38.8	0.54	16.2±29.2	0.72
	Single	63.8±4.8		91.7±5.6		37.5±47.9		12.5±14.4	
	Widow/widower	45±14.1		55.6±31.4		0±0		0±0	
Education	Illiterate	27.9±18.7	0.37	55.6±31.4	0.65	3.6±9.4	0.46	3.6±9.4	0.47
	Literate	65±52.2		66.7±57.7		41.7±52		33.3±38.2	
	Elementary school	56.4±44.3		68.3±34.2		28.6±48.8		21.4±36.6	
	High school	63.8±4.8		88.9±9.1		12.5±25		6.3±12.5	
	University	47.5±31.8		72.2±23.6		50±70.7		12.5±17.7	
Occupation	Seasonal agricultural worker	5	0.49	0	0.15	0	0.55	0	0.72
	Employee	41.7±52		70.4±25.7		0±0		0±0	
	Housewife	44.6±33.9		62.4±33.5		19.2±37		15.4±28	
	Self-employment	80±28.3		94.4±7.9		50±70.7		37.5±53	
	Student	65±5		92.6±6.4		50±50		16.7±14.4	
	Other	70		77.8		0		0	
Place of residence	Province/city	41.5±31.3	0.48	70.1±30.9	0.79	21.2±38	0.5	11.5±21.9	0.34
	District	60±37.7		55.6±38.5		0±0		0±0	
	Town/village	59.3±39.1		69.8±37.2		32.1±47.2		25±35.4	

study, we also determined, in agreement with previous studies, lower HRQoL scores in patients with CHC compared to healthy controls. We observed statistically significant differences in physical functioning, physical role limitations, energy/vitality and general health scores in these patients compared to controls. Pojoga et al. (27) reported that patients with CHB had better general health, social functioning and mental health scores than patients with CHC. Another study showed a significant decrease in HRQoL scores in patients with hepatitis C compared to that in patients with CHB (12). In our study, although HRQoL scores in patients with CHC were lower than those in patients with CHB, the difference was only statistically significant in emotional role limitations scores. Lower HRQoL scores observed in patients with CHC compared to those with CHB may be attributed to symptoms such as lethargy and fatigue being more pronounced in the former and to this then affecting their emotional scores. When we compared the HQRoL scores of patients with CHC during the treatment period with those of the control group, we determined a significant difference. This difference consisted of significantly low physical functioning, physical role limitations, emotional role limitations, mental health and vitality/energy scores in patients with hepatitis C at the 3rd month of treatment and also a significantly lower social functioning score in addition to the other parameters at the 6th. HRQoL in chronic hepatitis is adversely affected during treatment. This may be due to drug side-effects such as fatigue, flu-like findings, such as myalgia, and changes in psychological state, concentration impairment and loss of libido adversely impacting patients' energy and social functioning (28,29). Marcellin et al. (30) investigated HRQoL in patients with CHB and CHC receiving PEG-IFN α-2a therapy and reported better HRQoL scores, particularly in the physical component, in patients with hepatitis B compared to those with hepatitis C. In our study, HRQoL scores during treatment were better in patients with CHB than in those with CHC. The decrease in physical functioning and social functioning scores in patients with CHC at the 6th month was statistically significant. HRQoL during treatment being lower in patients with CHC than in patients with CHB may be associated with the side-effects of combined IFN and ribavirin therapy. We also determined a significant decrease in HRQoL scores during treatment in our patients with CHB compared with the control group. This decrease was statistically significant at the 6th month in physical, physical role limitations, emotional role limitations and energy/vitality scores.

Conclusion

Chronic viral hepatitis is a social health problem in Turkey. Chronic diseases can adversely affect quality of life in various ways. Patients with chronic hepatitis are exposed not only to the chronic effects of the disease, but also to undesirable effects of

Table 5. Continued

Before treatment									
		Mental health		Energy		Bodily pain		General health	
		Avg. ± SD	p	Avg. ± SD	p	Avg. ± SD	p	Avg. ± SD	p
6th month of Treatment									
Gender	Male	41.7±23.4	0.63	30±25.2	0.92	69.8±32.5	0.07	56±28.7	0.97
	Female	46±17.2		31.3±29		42.4±31.5		55.6±22.5	
Marriage status	Married	38.4±17.3	0.008	31.2±30.4	0.95	50.3±34.9	0.33	53.7±26.7	0.75
	Single	68±3.3		32.5±10.4		66.7±28.7		58.4±14.8	
	Widow/widower	52±5.7		25±35.4		22.2±15.7		67.3±12.4	
Education	Illiterate	40±12	0.31	14.3±19.9	0.45	34.9±36	0.66	48.9±28.1	0.7
	Literate	46.7±32.3		40±36.1		51.9±25.7		47±17.8	
	Elementary school	37.7±16.8		38.6±35.8		55.6±32.7		57.9±26.6	
	High school	62±9.5		40±16.8		66.7±28.7		69.9±22.2	
	University	48±33.9		30±0		55.6±62.9		56.3±8.8	
Occupation	Seassonal agricultural worker	12	0.004	0	0.74	22.2	0.61	27.5	0.45
	Employee	22.7±6.1		23.3±20.8		51.9±44.9		49.2±32.1	
	Housewife	44.3±15.6		30±32.1		44.4±33.6		54.1±24	
	Self-employment	58±8.5		40±28.3		61.1±23.6		66.8±9.5	
	Student	69.3±2.3		36.7±7.6		63±33.9		57.8±18.1	
	Other	48		60		100		96	
Place of residence	Province/city	45.8±18.6	0.63	19.2±22.3	0.05	43.6±30.6	0.26	48.7±22.5	0.15
	District	34.7±20.1		40±10		40.7±51.3		52±24.4	
	Town/village	46.9±20.4		48.6±31.8		68.3±29.7		70.2±22.8	

Avg: Average. SD: Standard deviation

IFN treatment and antiviral drugs. Measuring and evaluating quality of life is even more important in this patient group, in which severe decreases may be anticipated. Patients' quality of life is adversely affected by side-effects of treatment. This discomfort caused by treatment may also impair patients' compliance and willingness to continue with therapy. Emotional changes during treatment must be monitored and treatment should be provided when required. Considering the changes occurring in emotional and psychological states, psychiatric evaluation at least once during follow-up may be useful. Provision of counseling and guidance services can improve quality of life of patients with chronic viral hepatitis. Good standardization of HRQoL measures and application to patients with chronic diseases will identify negativities emerging and perhaps also be of assistance in coping with them.

Ethics

Ethic Committee Approval: The study was approved by Ataturk University Faculty of Medicine Ethics Committee (approval number: 65/2008).

Informed Consent: Informed consent was received from all.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

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Research Article

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Doi: 10.4274/vhd.2018.0002
Viral Hepatitis Journal 2018;24(2):43-46

Aspirin for Preventing Hemodialysis-associated Chronic Hepatitis C Infections

Hemodiyaliz İlişkili Kronik Hepatit C Enfeksiyonlarına Karşı Korunmada Aspirin

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ABSTRACT

Objectives: This study aimed to evaluate whether aspirin therapy is effective in protecting against hepatitis C virus (HCV) infection in maintenance hemodialysis patients, one of the high-risk groups for HCV infection.

Materials and Methods: This retrospective cross-sectional study included 408 patients with end-stage renal failure who underwent maintenance hemodialysis for at least 3 months in four private hemodialysis units in Hatay, Turkey, in January 2017. The patients were classified into two groups according to their aspirin exposure status: non-users (n=228) and regular aspirin users (n=180). The proportion of patients with hemodialysis-related chronic hepatitis C (CHC) was compared between the groups. Irregular aspirin users, patients infected with HBV or diagnosed with CHC before initiation of hemodialysis therapy were excluded from the study.

Results: The prevalence of hemodialysis-related CHC was 3.9% among the 408 patients. Hemodialysis-related CHC was not seen in any of the 180 regular aspirin users. Regular aspirin users showed a significantly lower prevalence of hemodialysis-related CHC than non-users (p<0.001). There was a significant (p<0.001), but weak (Cramer's V=0.180) correlation between hemodialysis-related CHC and aspirin exposure status.

Conclusion: These results indicated that regular use of aspirin might be linked to a lower risk of hemodialysis-related CHC. However, further prospective studies are required to confirm this association.

Keywords: Aspirin, chronic hepatitis C, hemodialysis

ÖZ

Amaç: Bu çalışmada hepatit C virüs (HCV) enfeksiyonu için yüksek risk gruplarından biri olan rutin hemodiyaliz hastalarında aspirin tedavisinin HCV enfeksiyonuna karşı korunmada etkili olup olmadığının değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Bu retrospektif kesitsel çalışma, Ocak 2017'de Hatay'da bulunan 4 özel hemodiyaliz merkezinde son dönem böbrek yetmezliği nedeniyle en az 3 ay süre ile rutin hemodiyaliz tedavisi almış olan 408 hastayı içermekte idi. Hastalar aspirin kullanım durumlarına göre iki gruba ayrıldı: İlk grup hemodiyaliz başlangıcından itibaren hiç aspirin kullanmamış 228 hastadan, ikinci grup ise hemodiyaliz başlangıcından itibaren düzenli aspirin kullanmakta olan 180 hastadan oluşmakta idi. Hemodiyaliz ilişkili kronik hepatit C (KHC) oranları gruplar arasında karşılaştırıldı. HBV ile enfekte, hemodiyaliz tedavisi öncesinde KHC tanısı almış olan, düzensiz aspirin kullanan hastalar çalışmaya dahil edilmedi.

Bulgular: Hemodiyaliz ilişkili KHC prevalansı toplam 408 hastada %3,9 idi. Düzenli aspirin kullanımı olan 180 hemodiyaliz hastasının hiçbirinde hemodiyaliz ilişkili KHC görülmedi. Düzenli aspirin kullanıcılarında hemodiyaliz ilişkili KHC prevalansı hiç aspirin kullanmamış hastalarla karşılaştırıldığında anlamlı oranda daha düşük bulundu (p<0,001). Aspirin kullanım durumu ile hemodiyaliz ilişkili KHC arasında anlamlı (p<0,001), ancak zayıf (Cramer's V=0,180) bir korelasyon bulunmakta idi.

Sonuç: Bu sonuçlar düzenli aspirin kullanımının hemodiyaliz ilişkili KHC riskinin azaltılmasında yararlı olabileceğini düşündürmektedir. Bununla birlikte, bu varsayımı doğrulamak için daha ileri prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Aspirin, kronik hepatit C, hemodiyaliz

Bal T, Önlen Y, Şahin Sİ, Turgut FH. Aspirin for Preventing Hemodialysis-associated Chronic Hepatitis C Infections. Viral Hepat J. 2018;24:43-46.

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Introduction

Hepatitis C is a global health problem affecting an estimated 2.35% of the world population, and individuals undergoing maintenance hemodialysis (HD) are known to have a 5-fold greater risk of hepatitis C compared with the general population (1,2). Moreover, it has been reported that the presence of hepatitis C might be associated with increased mortality and graft rejection in end-stage renal disease patients undergoing HD or kidney transplantation (3).

Despite improvements in the treatment of chronic hepatitis C (CHC) in HD patients, this infection remains significant in HD patients as current treatments cannot prevent re-infections and there is currently no vaccine to prevent hepatitis C (4). Therefore, there is a need for alternative protective measures for the prevention of hepatitis C in HD patients.

Aspirin, also known as acetylsalicylic acid is a cyclooxygenase-1 (COX-1) and -2 (COX-2) inhibitor which has an antiviral effect on RNA viruses, including hepatitis C virus (HCV) (5,6). In recent years, *in vivo* and *in vitro* studies have shown that the use of aspirin increases the efficacy of standard antiviral therapy by suppressing HCV replication, slowing the progression of liver damage and preventing hepatocellular carcinoma development in CHC patients (7,8,9). Consistent with these data, Manning et al. (7) showed that successful antiviral therapy resulted in the normalisation of COX-2 over-expression which was induced by HCV infection. Claudin-1 is a tight junction protein which is highly expressed in the liver and known to be an essential factor for HCV entry (10). In a more recent study of the antiviral effect of aspirin, Yin et al. reported that aspirin inhibited the entry of HCV by decreasing the expression of claudin-1 (11).

According to the results of these studies, it was hypothesised that aspirin use may be effective in preventing HCV infections/re-infections in maintenance HD patients who have an increased risk for HCV infection. The aim of this study was therefore to investigate whether aspirin use is effective in the prevention of HCV infection in maintenance HD patients.

Materials and Methods

We conducted a cross-sectional retrospective study in January 2017 at four private HD units in Hatay, Turkey. A total of 408 patients with end-stage renal failure undergoing maintenance HD for at least three months were enrolled. Inclusion criteria for this study were (1) maintenance HD for at least three months. Exclusion criteria were (1) diagnosis of CHC before initiation of HD therapy, (2) being infected with hepatitis B (3) irregular aspirin use (<3 days per week), and (4) age <18 years. The participants were interviewed and the following data were obtained using a standardised questionnaire and were checked from medical records: presence of HBV infection, a history of drug abuse, blood transfusion(s) or renal transplantation, aspirin exposure information (dose, the frequency of use) and the date of initiation of HD. In Turkey, HD patients are examined routinely every three months for viral hepatitis and patients with positive anti-HCV are also tested for HCV RNA. Thus, serum anti-HCV and HCV RNA results since the initiation of HD were obtained from medical records retrospectively. The positivity of anti-HCV and HCV RNA for at least six months was defined as CHC. Patients diagnosed with CHC after initiation of HD therapy were defined as having HD-related CHC.

The patients were classified in two groups (regular aspirin users and non-users) based on aspirin exposure status since the initiation of HD. These exposure categories were selected according to prior studies showing that the antiviral effect of aspirin for HCV was time-dependent and was highest at 72 hours post-treatment (12). Regular aspirin use was defined as use of any dose of aspirin at least 3 times per week from the initiation of HD for at least 3 months. Patients, who reported no aspirin use, were defined as non-users. The presence of HD-related CHC, the duration of HD, the rate of patients with a history of blood transfusion or renal transplantation were compared between the two groups.

Low-dose aspirin was defined as a dose of 100-150 mg and high-dose aspirin was defined as a 300 mg dose.

To control microbial contamination of dialysis machines, hot-water (at 80 °C) rinsing was applied after each dialysis session and chemical disinfection was performed at the end of the day and at the end of the week. Disposable dialysis kits and needle sets were used and standard precautions, such as hand hygiene, personal protective equipment, and disinfection of equipments and surfaces, were followed. All patients positive for hepatitis B surface antigen and anti-HCV were dialyzed on dedicated dialysis machines in separate rooms. These standard precautions and practices were applied to control infection in each of four HD units.

Statistical Analysis

SPSS software package was used for statistical analyses (version 23.0, Chicago, IL, USA). Histograms, probability plots and the Kolmogorov-Smirnov/Shapiro-Wilk tests were used for testing of distribution normality. To compare variables between the two groups, the Mann-Whitney U test was used to compare non-normally distributed variables and chi-square test/Fisher's exact test (where appropriate) for categorical variables. The correlation between aspirin exposure status and the percentage of HD-related CHC were tested using the chi-square test of Independence. A p-value of less than 0.05 was considered statistically significant.

Results

The study included 228 non-users and 180 regular aspirin users. Of the 408 patients, 58.3% were female and 41.7% were male. The median age of the patients was 60.3 (18-95) years. The median duration of HD was 52 (3-336) months. In the total of 408 patients, the prevalence of HD-related CHC was 3.9%. The patients' characteristics are shown in Table 1.

None of the patients had a history of intravenous drug abuse or tattooing.

The most striking result to emerge from the data was that HD-related CHC infection was not seen in any of the 180 patients who had been receiving aspirin therapy regularly since the initiation of HD.

The chi-square test of independence showed a significant ($p<0.001$), but weak (Cramer's $V=0.180$) correlation between HD-related CHC and aspirin exposure status.

The proportion of patients with HD-related CHC was significantly lower in the regular aspirin user group than in the non-user group, although patients in the regular aspirin user group were older and

had a longer duration of HD (in months) than those in the non-user group. In addition, there was no significant difference in the proportion of patients with HD-related CHC between the groups when the patients are classified according to the duration of HD (in months) (p=0.179) (Table 2).

To analyze any association between aspirin dose and the risk of HD-related CHC, drug exposure data was obtained. Most patients (86.6%) were using low dose (100-150 mg) aspirin.

Discussion

In this study, it was investigated whether regular aspirin use was effective in preventing HCV infection in maintenance HD patients. The results indicate that regular use of aspirin may be associated with a decreased risk of HD-related CHC. Previous studies have reported that the expression of HCV proteins increase intracellular reactive oxygen species levels (13). Moreover, a number of authors have reported that antioxidants, including aspirin, modulate the oxidative stress induced by HCV at the same time by decreasing viral replication as well as decreasing viral protein expression. It has been suggested that the antiviral activity of aspirin might be mediated by the modulation of oxidative stress (14,15). Overall, there seems to be some evidence to suggest that aspirin has an antiviral effect against HCV. However, there are only limited data on the prophylactic effect of aspirin against HCV. These results therefore need to be interpreted with caution and large randomised controlled trials could provide more definitive evidence.

Although most studies in the field of the antiviral effect of aspirin have focused on controlling viral replication and protein expression, to the best of our knowledge, a pre-clinical study by Yin et al. is the only one which has directly investigated the potential prophylactic role of aspirin in HCV infection (11). The authors revealed that aspirin inhibited the entry of HCV by decreasing the expression of claudin-1, which is a tight junction protein that is highly expressed in the liver and an essential factor for HCV entry (10,11,14,16). This also concurs with previous reports, which showed that aspirin had an anti-HCV effect through down regulation of HCV protein expression (12,16). In the current study, the most important clinically relevant finding was that HD-related CHC infection was not seen in any of the patients who had been receiving aspirin therapy regularly since the initiation of HD. The present findings seem to be consistent with those of Yin and Zhang (11) and indicate that regularly taking aspirin every other day could protect against CHC infection in maintenance HD patients. This is also consistent with earlier observations, which showed that the antiviral effect of aspirin was still maximal 3 days after the last administration and the antiviral effect of aspirin was highest at 72 hours post-treatment, because we defined the regular aspirin use as any dose of aspirin ≥3 days per week in the current study (12). Nevertheless, because of the retrospective nature of the study and small number of HD-related CHC cases this result should be interpreted with caution. Further research on this topic is required to confirm these speculations.

COX-2 has been shown to be over-expressed in patients with CHC (7). Recent *in vitro* studies have speculated that COX-2 activity may be involved in aspirin-mediated down regulation of viral replication and protein expression (12,16). Even though aspirin has a very short half-life in plasma, aspirin irreversibly inactivates the COX activity of the platelets and the platelet reactivity has been seen to be normalized 96 hours after the cessation of a single oral dose of 100 mg aspirin (5,17). However, it is unclear whether the antiviral effect of aspirin also continues for 96 hours. Further experimental investigations are needed to determine when this antiviral activity of aspirin disappears after the last dose of aspirin intake in HD patients.

In an investigation of the anti-HCV effect of aspirin, the researchers found that aspirin had a dose-dependent antiviral effect (12). Therefore, to clarify any association between aspirin dose and the risk of HD-related CHC, drug exposure data was obtained.

Table 1. Characteristics of each group and statistical differences between groups

		Non-user group (n=228)	Regular aspirin user group (n=180)	p
Age, median (IQR)		60.5 (18-95)	63 (21-89)	0.005[a]
Gender	Male (%)	56.1	61.1	0.312[b]
	Female (%)	43.9	38.9	
Duration of hemodialysis (in months)		48 (3-336)	72 (3-168)	0.020[a]
Presence/proportion of hemodialysis related CHC, n (%)		16 (3)	0 (0)	<0.001[b]
Blood transfusion(s), n (%)	Yes	71 (31.1)	66 (36.7)	0.241[b]
	No	157 (68.9)	114 (63.3)	
Renal transplantation, n (%)	Yes	23 (10.1)	13 (7.2)	0.311[b]
	No	205 (89.9)	167 (92.8)	

[a]Mann-Whitney U test, [b]Chi-square test, IQR: Interquartile range, CHC: Chronic hepatitis C

Table 2. Comparison of the presence of hemodialysis related chronic hepatitis C between the groups according to the duration of hemodialysis

	Hemodialysis related CHC (+)		Hemodialysis related CHC (-)		p
	Regular aspirin users	Non-users	Regular aspirin users	Non-users	
Duration of hemodialysis ≤84 months	0	9	159	166	0.179[a]
Duration of hemodialysis >84 months	0	7	18	46	-

[a]Chi-square test, CHC: Chronic hepatitis C

However, probably because the HD population is at high risk of bleeding events, most patients were using low-dose aspirin (18). Overall, each dose category (low and high-dose) was too small to provide valid results. Therefore, it was not possible to investigate whether there was a relationship between the dose of aspirin and the risk of HD-related CHC. There is a need for further research on this topic to provide a better understanding of the optimal dose of aspirin to reduce the risk of CHC.

Study Limitations

Finally, a number of important limitations need to be considered. First, the major limitation was the small number of HD-related CHC cases. Secondly, there was no information about the total number of blood transfusion units since initiation of HD, which may have increased the risk of HD-related CHC infection. The retrospective nature of the study was another limitation. Despite these limitations, this research is the first clinical trial testing the hypothesis that aspirin has a prophylactic effect against CHC in a high-risk group, such as the group of HD patients included here. The results of this research provide further support for the hypothesis that the use of aspirin has an antiviral effect against HCV and reduces the risk of CHC.

Conclusion

Although the current study is based on a small sample of participants, the findings suggested that a regular every other day regimen of low-dose aspirin in maintenance HD patients might reduce the risk of CHC. Nevertheless, there is a need for further large-scale prospective studies to confirm these findings.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Mustafa Kemal University, Faculty of Medicine, Hatay, Turkey (decision date: 09.02.2017, decision number: 12).

Informed Consent: Informed consent was not necessary because of the retrospective design of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.B., Design: T.B., Y.Ö., S.İ.Ş., F.H.T., Data collection or Processing: T.B., Y.Ö., S.İ.Ş., F.H.T., Analysis or Interpretation: T.B., Y.Ö., S.İ.Ş., F.H.T., Literature Search: T.B., Writing: T.B.

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

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

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Research Article

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Doi: 10.4274/vhd.2018.0005
Viral Hepatitis Journal 2018;24(2):47-52

Analysis of Virological, Histological and Clinical Features of Hepatitis Delta Virus Infection in Southeastern Turkey

Güneydoğu Anadolu Bölgesi'ndeki Delta Hepatit Virüs Enfeksiyonlu Hastalarımızın Virolojik, Histolojik ve Klinik Özelliklerinin Analizi

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ABSTRACT

Objectives: The present study aims to investigate biochemical, virological and histological characteristics of hepatitis delta virus infection, which is a serious problem in our region, as well as its relationship with chronic hepatitis B virus (HBV) infection and cirrhosis.

Materials and Methods: A total of 220 patients were included in the study. The patients were divided into three groups: group 1 included patients with hepatitis delta virus-related cirrhosis (DA cirrhosis), group 2 consisted of patients with chronic delta hepatitis (CHD) and group 3 composed of patients with chronic hepatitis B (CHB). Biochemical and virological parameters of the patients were analyzed. Patients with CHB and CHD underwent biopsy for histological examination. The results were compared among the three groups.

Results: Seventy-five (34.09%) of the patients were women, 145 (65.90%) were males and their mean age was 38.04 years. There were 44 patients (20%) with delta hepatitis-associated cirrhosis, 86 patients with CHD (39.09%) and 90 patients with CHD (40.9%). HBV DNA level was significantly lower in patients with cirrhosis and chronic delta hepatitis than in patients with CHB (p<0.001) (p<0.001). Histology activity score and fibrosis stage were significantly higher in CHD than in CHB (p<0.001) (p<0.001). A significant correlation was determined between fibrosis stage and hepatitis delta virus RNA in CHD patients. There was also a significant correlation between necroinflammatory score and alanine aminotransferase in CHD (p=0.021).

Conclusion: In Turkey, the age of onset of delta hepatitis is low and accordingly, related liver cirrhosis develops at a younger age. HBV DNA levels appear to be suppressed in patients with delta hepatitis as compared to patients with CHB. Histologically severe disease picture is seen in patients with delta hepatitis and delta hepatitis-positive cirrhotic patients.

Keywords: Hepatitis delta virus, hepatitis B virus, cirrhosis, liver biopsy

ÖZ

Amaç: Hepatitis delta virüsü replikasyonu için hepatit B yüzey antijenine ihtiyaç duyan defektif bir virüstür. Bu çalışmadaki amacımız bölgemizdeki delta hepatitli hastaların virolojik, histolojik ve biyokimyasal özelliklerini araştırmaktır.

Gereç ve Yöntemler: Toplam 220 hasta çalışmaya alındı. Hastalar üç grupta incelendi: delta hepatite bağlı siroz (Dİ siroz), kronik delta hepatit (CHD) ve kronik hepatit B (CHB). Kronik delta ve hepatit B grubundaki hastaların biyopsilerindeki histolojik özellikleri incelendi. Üç grubun özellikleri karşılaştırıldı.

Bulgular: Hastaların 75'i (%34,09) kadın, 145'i (%65,90) erkek ve ortalama yaşları 38,04 idi. Delta hepatite bağlı sirozlu 44 hasta (%20), CHD'li 86 hasta (%39,09) ve CHB'li 90 (%40,9) hasta vardı. Siroz ve kronik delta hepatitli gruplar arasında HBV DNA düzeyleri açısından anlamlı farklılık yoktu (p=0,466). Ancak bu iki grubun HBV DNA düzeyleri kronik hepatit B'li gruba göre anlamlı olarak düşüktü (p<0,001-p<0,001). CHD'nin histolojik aktivite ve fibrozis evresi CHB'den anlamlı olarak yüksekti (p<0,001) (p<0,001). CHD'deki hastaların HDV RNA değeri ile fibrozis evreleri arasında anlamlı korelasyon vardı. Bu grupta alaninamino transferaz ile histolojik aktivite arasında anlamlı korelasyon saptandı (p=0,021).

Sonuç: Türkiye'de delta hepatit başlangıç yaşı küçük olduğu için kronik karaciğer hastalığı da genç yaşta ortaya çıkar. Delta hepatit, delta ile ilişkili siroz ve hepatit B'li hastaların ALT düzeyi farklılıklar gösterir. HBV DNA seviyeleri, delta hepatitli hastalarda kronik hepatit B'li hastalarla karşılaştırıldığında baskılanmıştır. Histolojik olarak delta hepatit pozitif hastalarda daha ağır bir hastalık tablosu mevcuttur.

Anahtar Kelimeler: Hepatit delta virüs, hepatit B virüs, siroz, karaciğer biyopsisi

Yalçın MS, Yalçın K. Analysis of Virological, Histological and Clinical Features of Hepatitis Delta Virus Infection in Southeastern Turkey. Viral Hepat J. 2018;24:47-52.

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Introduction

Hepatitis delta virus (HDV) is a defective RNA virus. HDV causes co-infection and super infection by using hepatitis B virus (HBV) surface antigen (HBsAg). Today, HDV infection remains a serious health problem particularly in endemic regions (1). There are more than 240 million chronic carriers of HBV, and approximately 15 million of them have serological evidence of exposure to HDV, worldwide (2,3,4).

The prevalence of HDV infection in Europe has changed with the control of HBV infection achieved in the last 20 years (5). The current prevalence of HDV infection among HBsAg carriers is approximately 10% in Italy (6) and 11% in Turkey (7). In Turkey, HDV strains exhibit wide genetic diversity reflecting an ancient evolution and/or successive outbreaks (8). However, HDV still accounts for almost one half of overall cases of liver cirrhosis and hepatocellular carcinoma in southeastern Turkey (9).

Chronic HBV and HDV infections have wide range of clinical manifestations from the state of asymptomatic carrier to chronic active hepatitis, liver cirrhosis and hepatocellular carcinoma. However, underlying mechanisms of such clinical variety have not been fully defined yet (1). In the present study, we aimed to investigate biochemical, virological and histological parameters in HDV infection, which is a serious problem in our region, and to investigate its relationship with HBV and HDV viral loads. Within this context, our aim is to designate characteristic features of HDV and it will contribute to determining the follow-up, treatment and natural course of the disease.

Materials and Methods

The study included a total of 220 patients [75 (34.09%) females and 145 (65.90%) males] aged between 15 and 70 years, who were admitted to the gastroenterology and hepatology inpatient or outpatient clinics at Dicle University Faculty of Medicine Gastroenterology and Hepatology Department and fulfilled the inclusion criteria. Physical examination findings, results of laboratory tests for biochemical, hematological and virological parameters and HBV and HDV markers, and epidemiologic history of all patients were recorded.

Study Groups and Definition

Patients were grouped into three groups:

HDV-related cirrhosis (DA cirrhosis).

Chronic hepatitis delta (CHD) without cirrhosis.

Chronic hepatitis B (CHB) (without hepatitis D).

HBsAg-positive and anti-HBs-negative patients, who had undulating alanine aminotransferase (ALT) concentrations for at least 6 months were defined as CHB patients. Liver biopsy was performed in 45 patients in CHD and in 77 patients in CHB. Histopathological findings were recorded.

The present study was retrospective.

Eligibility Criteria

Treatment-naive patients or patients who did not receive treatment for at least six months were included in the study.

The diagnosis of liver cirrhosis was established based on laboratory, histological analysis or abdominal ultrasonography findings which demonstrated hepatic surface irregularity, caudate lobe hypertrophy, splenomegaly and injury to the hepatic parenchyma, and on the presence of esophageal varices confirmed by endoscopy. The group with active CHD consisted of patients with positive HBsAg and anti-delta antibody and negative anti-HBs for at least six months, with ALT/aspartate aminotransferase (AST) levels higher than 1.5 times the upper limit of normal, and moderate-to-severe active hepatitis shown by liver biopsy.

Exclusion Criteria

Patients with an accompanying infection with hepatitis C virus (HCV), non-hepatotropic viruses such as human immunodeficiency virus, herpes simplex virus, cytomegalovirus and Epstein-Barr virus, patients with heavy alcohol consumption (more than 8 drinks per week), those using drugs (that may induce hepatitis) and herbal medicines, and patients having autoimmune hepatitis, hepatic ischemia and pregnancy-related liver disease were excluded from the study.

Biochemical and Hematological Markers

Biochemical [albumin, globulin, lactic dehydrogenase, total bilirubin, ALT, AST, creatinine, glucose, alkalen phosphatase (ALP), gama glutamyltranspeptidase and alpha-fetoprotein (AFP)] and hematological (ferritin, serum iron, serum iron binding capacity, leukocyte, hemoglobin, platelet, and prothrombin time) parameters were analyzed in all patients. Biochemical parameters were analyzed using an Architect C16000 device and complete blood count was analyzed using an Abbott CELL-DYN 3700 device.

Serological and Virological Testing

The serological markers of HBsAg, anti-HBs, hepatitis B e (HBe) antigen and anti-HBe were tested by macro-ELISA method, whereas anti-delta immunoglobulin (Ig) M and anti-delta IgG were tested by micro-ELISA method. HDV RNA level was analyzed by real time reverse transcriptase polymerase chain reaction (PCR) (ABI-PRISM/7700 Sequence Detector, AJ RoboscreenGmBH, Germany) method, whereas HBV DNA was analyzed by COBAS Ampli Prep/CobasTaq Man HBV test (ROCHE, USA).

Liver Biopsy

Liver biopsy was planned for histological examination in patients with CHB and CHD. Fine needle biopsy was performed using the Menghini technique under the guidance of ultrasonography. All biopsies were stained with hematoxylin-eosin for grading necroinflammation and reticulin for the assessment of fibrosis. Biopsy materials were blindly evaluated by a single pathologist. Histologic scoring was done using the Ishak-modified histology activity index (10). Fibrosis was assessed according to Ishak fibrosis score. The Ishak system has more stages of fibrosis (0-6) when compared to other systems (11). Because of having the ability to differentiate milder changes in fibrosis more clearly, the Ishak staging system has been widely used in clinical trials (12).

Statistical Analysis

Statistical analysis was done by 'SPSS 16.0 for Windows' package program. The results were presented as mean ± standard deviation. Pearson's or Spearman's correlation coefficient was used to analyze correlations. A p value of less than 0.05 was considered statistically significant.

Results

Clinical and Demographic Data (Table 1)

A total of 220 patients with a mean age of 38.04 years, of whom 75 (34.09%) were female and 145 (65.90%) were male, participated in the study. In patients with DA cirrhosis; 16 (36.36%) of 44 patients were female and 28 (63.64%) were male with a mean age of 44.37±12.42 years. In patients with CHD; 31 (36.04%) of 86 patients were female and 55 (63.96%) were male with a mean age of 37.92 years. In patients with CHB; 28 (31.1%) of 90 patients were female and 62 (68.9%) were male with a mean age of 35.06 years. Demographic, biochemical and serological characteristics of these groups are shown in Table 1.

The mean age of the patients in DA cirrhosis was significantly higher than in CHD (p=0.006) and CHB (p<0.001).

Biochemical and Hematological Data

Analysis of biochemical and hematological data are shown in Table 1. ALP levels in DA cirrhosis were significantly higher than in CHB (p<0.001). ALP levels in CHD were significantly higher than in CHB (p=0.001). Serum albumin levels in DA cirrhosis patients were significantly lower than in CHD and CHB patients. Globulin levels in DA cirrhosis were significantly higher than in CHD (p<0.001). Globulin levels in DA cirrhosis was also significantly higher than in CHB (p<0.001). Ferritin levels in DA cirrhosis were found to be significantly higher than in CHD (p=0.032) and CHB (p=0.010); whereas, no significant difference was found when CHD was compared with CHB (p=0.848). AFP levels in DA cirrhosis were significantly higher than in CHD (p=0.029) and CHB (p<0.001); whereas, no significant difference was found between CHD and CHB (p=0.270). Distribution of demographic, biochemical, hematological and virological characteristics of study participants among groups are shown in Table 1.

Serological Data

HBV DNA levels in DA cirrhosis group were significantly lower than in CHB group (p<0.001). HDV RNA levels were found to be 4.35±1.41 (Log_{10}) copies/mL in patients with DA cirrhosis and 4.69±1.63 (Log_{10}) copies/mL in patients with CHD. No significant

Table 1. Univariate analysis of demographic, biochemical and hematological parameters of all patient groups

Variable	Group 1: HDV related liver cirrhosis (n=44)	Group 2: Chronic delta hepatitis (n=86)	Group 3: Chronic hepatitis B (n=90)	p (1-2)	p (1-3)	p (2-3)
Age	44.37±12.42	37.92±12.07	35.06±9.53	0.006	<0.001	0.208
Gender (F/M)	16/28	31/55	28/62	-	-	-
ALT (U/L)	83.64±62.98	94.83±100.37	80.57±60.56	0.725	0.976	0.456
AST (U/L)	96.14±73.90	70.21±112.61	50.50±45.29	0.213	0.009	0.259
ALP (U/L)	118.00±54.46	103.12±47.10	79.51±25.98	0.134	<0.001	0.001
GGT (U/L)	96.14±109.50	62.76±56.79	59.73±122.13	0.167	0.115	0.978
Albumin (g/dL)	3.26±0.53	4.02±0.43	4.12±0.35	<0.001	<0.001	0.321
Globulin (g/dL)	4.53±0.92	3.87±0.78	3.43±0.48	<0.001	<0.001	<0.001
T.Bilirubin (mg/dL)	1.72±1.34	1.00±1.55	0.82±0.55	<0.001	<0.001	<0.001
Creatinine (mg/dL)	0.80±0.20	0.85±0.19	0.89±0.19	0.353	0.025	0.289
Glucose (mg/dL)	112.11±46.65	102.22±38.85	94.83±23.19	0.286	0.022	0.348
LDH (U/L)	251.36±118.92	209.43±97.98	206.94±92.57	0.065	0.045	0.985
Hemoglobin (g/dL)	12.54±2.04	14.32±1.68	14.74±1.66	<0.001	<0.001	0.260
Leukocyte (mm^3)	4559.09±2172.68	6221.77±2108.35	6787.67±1492.03	<0.001	<0.001	0.119
Platelet (mm^3)	87281.82±40736.11	173096.51±56620.97	226788.89±55345.39	<0.001	<0.001	<0.001
INR	1.39±0.23	1.23±0.96	1.04±0.14	0.339	0.007	0.113
Iron (u/dL)	90.33±53.97	101.34±46.24	103.93±46.65	0.440	0.290	0.935
SIBC (u/dL)	227.49±116.96	252.45±85.46	228.39±79.02	0.305	0.998	0.201
Ferritin (u/dL)	293.25±483.88	156.33±186.00	131.85±232.99	0.032	0.010	0.848
AFP	8.44±9.48	4.97±8.17	3.23±4.12	0.029	<0.001	0.270
HBV DNA Log_{10} (IU/mL)	3.42±1.05	3.84±1.09	5.31±1.70	0.466	<0.001	<0.001
HDV RNA Log_{10} (copies/mL)	4.35±1.41	4.69±1.63	-	0.335	-	-
Necroinflammation score, grade	-	9.30±2.89	5.95±2.82	-	-	<0.001
Fibrosis stage	-	3.14±1.24	1.94±1.40	-	-	<0.001

Note: P (1-2): p value of comparison for group 1 and 2; P (1-3): p value of comparison for group 1 and 3; P (2-3): p value of comparison for group 2 and 3.
F: Female, M: Male, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkalen phosphatase, GGT: Gama glutamyltranspeptidase, T.Bilirubin: Total bilirubin, LDH: Lactic dehydrogenase, INR: International normalized ratio, SIBC: Serum iron binding capacity, AFP: Alpha-fetoprotein, HBV: Hepatitis B virus, HDV: Hepatitis delta virus

difference was found between these two groups in terms of HDV RNA levels (p=0.335). Virological characteristics of study participants are shown in Table 1.

Histological Data

Based on the liver biopsy findings of the study participants, the mean histological activity score (necroinflammation), which was calculated according to Ishak's scoring system, was 9.30±2.89 in CHD and 5.95±2.82 in CHB. It was significantly higher in CHD than in CHB (p<0.001). Comparing the fibrosis stage between CHD and CHB, CHD patients had higher fibrosis stage than CHB patients (p<0.001). Histopathological findings of the study participants are shown in Table 1.

Correlation Analysis

A significant correlation was found between fibrosis stage and HDV RNA levels (r=0.572, p=0.002) (Figure 1). No significant correlation was found between HDV RNA and ALT and AST levels (p=0.743 and p=0.347, respectively).

A significant correlation was found between necroinflammation score and ALT in CHD (r=0.350, p=0.021). The results of correlation analysis in CHD group are shown in Table 2.

HBV DNA levels were significantly correlated with both ALT (r=0417, p<0.001) (Figure 2) and AST levels (r=0.344, p=0.001) (Figure 3) in CHB group. HBV DNA levels were not correlated with necroinflammation scores (r=0.139, p=0.237) and fibrosis stage (r=0.141, p=0.231) in CHB. ALT levels were significantly correlated with necroinflammation score (r=0.290, p=0.010); however, no significant correlation was found between ALT levels and fibrosis stage (r=0.191, p=0.096). While AST levels were correlated with necroinflammation score (r=0.385, p=0.001); it was not correlated with fibrosis stage (r=0.193, p=0.092). The results of correlation analysis in CHB are shown in Table 3.

Discussion

HDV is a defective RNA virus and causes infection using HBsAg. There have been a limited number of studies investigating factors playing a role in clinical manifestations and events observed during natural history of the disease in patients with CHD and the dominant virus in the progression of disease. In the present study, we aimed to investigate clinical, virological and histological characteristics of patients with CHD and with HDV-positive cirrhosis and to compare with those in patients with CHB.

In their study including 48 HBsAg- and anti HDV-positive patients, Yamashiro et al. (13) reported that the mean age of cirrhotic patients (65.9±9.3 years) was higher than that of asymptomatic patients (61.8±16.4 years) and patients with CHD (54.2±12.0 years) (p<0.05 and p<0.05, respectively). Wu et al. (14) reported in their study including 185 patients that the mean age was 43±16 years in patients with CHD and 54±10 years in cirrhotic patients. In our study the mean age of patients in DA cirrhosis, CHD and CHB was 44.37±12.42 years, 37.92±12.07 years and

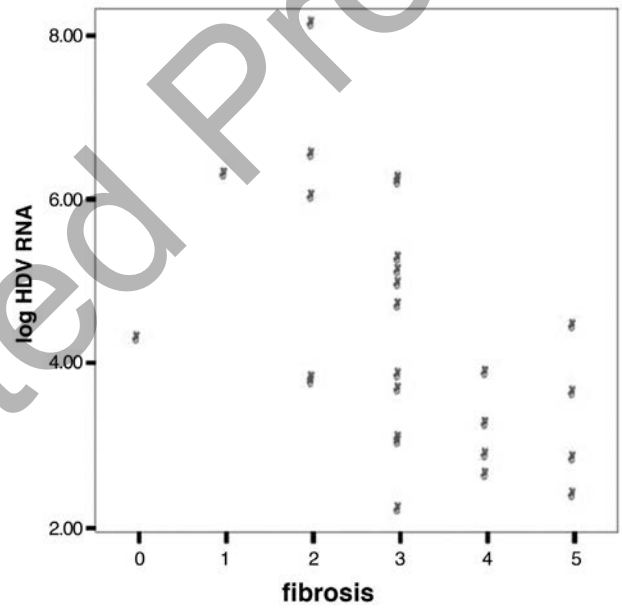

Figure 1. Relation between Log hepatitis delta virus RNA and fibrosis stage in chronic delta hepatitis group (r=0.572, p=0.002)
HDV: Hepatitis delta virus

Table 2. Results of correlation analysis in the patients with chronic hepatitis D

		Log HDV RNA	Log HBV DNA
Spearman's rho NIA	Corr. coefficient p n	0.350 p=0.08 26	0.079 p=0.691 28
Stage	Corr. coefficient p n	0.572 (**) p=0.002 26	0.046 p=0.815 28
ALT	Corr. coefficient p n	0.049 p=0.743 47	0.198 p=0.168 50
AST	Corr. coefficient p n	0.140 p=0.347 47	0.222 p=0.121 50

**Correlation is significant at the level of 0.01 (2-tailed), *Correlation is significant at the level of 0.05 (2-tailed)
HBV: Hepatitis B virus, HDV: Hepatitis delta virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, N/A: Not applicable

Table 3. Results of correlation analysis in the patients with chronic hepatitis B

		Log HBV DNA
ALT	Pearson correlation p n	0.417 (**), p<0.001 87
AST	Pearson correlation p n	0.344 (**), p<0.01 87
NIA	Pearson correlation p n	0.139 p=0.237 74
Stage	Pearson correlation p n	0.141 p=0.231 74

**Correlation is significant at the level of 0.01 (2-tailed), *Correlation is significant at the level of 0.05 (2-tailed)
HBV: Hepatitis B virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, N/A: Not applicable

35.06±9.53 years, respectively. Cirrhotic patients were older than non-cirrhotic subjects (p<0.01), consistent with previous studies. On the other hand, we have found that the mean age of patients with DA cirrhosis was lower than reported in previous studies. This difference arises from the presence of higher number of new cases among study participants and indicates perinatal transmission of both viruses HBV and HDV. Therefore, it indicates the importance of vaccination against HBV in eradication of delta hepatitis.

Yamashiro et al. (13) reported that there was no statistically significant difference in mean ALT levels between patients with CHD and those with cirrhosis (130.7±214.1 and 84.4±65.3, respectively) but asymptomatic patients had significantly lower ALT levels as compared to CHD group (p<0.05) and cirrhosis group (p<0.05). Wu et al. (14) reported higher ALT levels than in our study. In our study, AST level was found to be significantly higher in DA cirrhotic patients as compared to the group with CHB (p=0.009). We also found that the albumin level was significantly lower in DA cirrhosis as compared to non-cirrhotic patients (p<0.001). No significant difference was found between patients with CHD and CHB (p=0.321). This result supports the previous study of Yamashiro et al. (13) because in that study, albumin level was not found to be statistically significantly different between cirrhosis (4.4±0.8), CHD (4.5±0.5) and asymptomatic (4.5±0.5) patient groups. In the present study, platelet count was found to be significantly lower in cirrhotic patients as compared to that in patients with CHD and patients with CHB infection (p<0.001, p<0.001). Platelet count was significantly lower in the CHD as compared to the CHB patients (p<0.001). These results appear to support the results of a similar study existing in the literature (13).

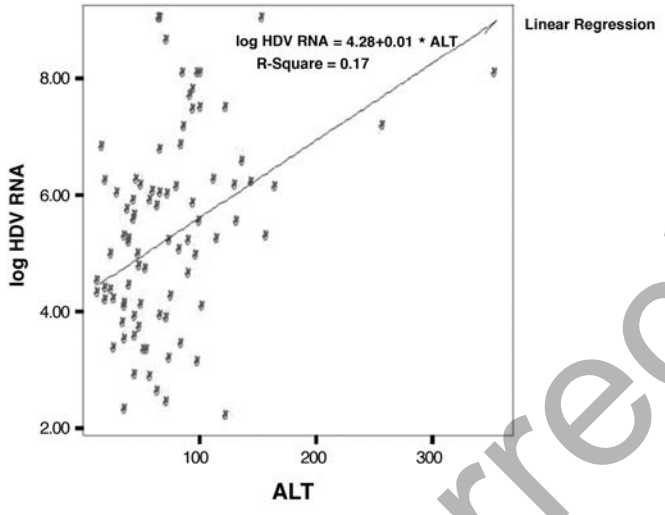

Figure 2. Relation between Log hepatitis B virus DNA and alanine aminotransferase in chronic hepatitis B group
ALT: Alanine aminotransferase, HDV: Hepatitis delta virus

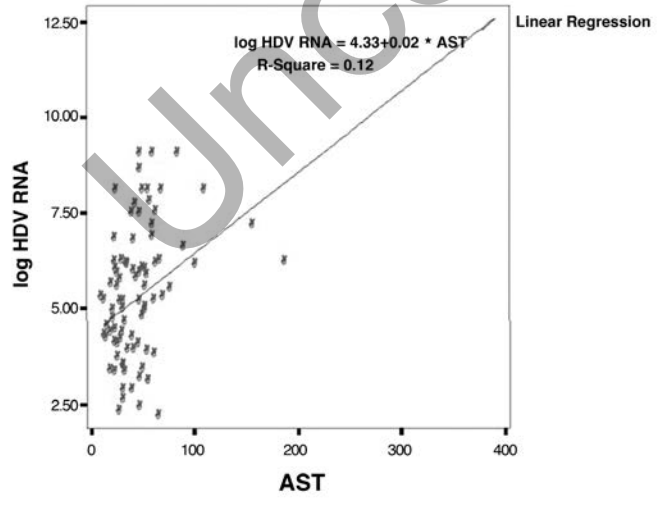

Figure 3. Relation between log hepatitis B virus DNA and aspartate aminotransferase in chronic hepatitis B group
AST: Aspartate aminotransferase, HDV: Hepatitis delta virus

In the present study, there was no statistically significant difference in HBV DNA level between patients of DA cirrhosis (3.42±1.05 Log_{10} copies/mL) and CHD (3.84±1.09 Log_{10} copies/mL) (p=0.466). However, HBV DNA levels in DA cirrhosis patients were significantly lower as compared to patients with CHB (5.31±1.70) (p<0.001). Likewise, HBV DNA levels in patients with CHD were found to be significantly lower as compared to that in patients with CHB infection (p<0.001). HDV RNA level was not significantly different between patients with DA cirrhosis and patients with CHD (p=0.335). Yamashiro et al. (13) found no difference between the patient groups (asymptomatic, chronic hepatitis and cirrhosis) in terms of HBV DNA levels. Wu et al. (14) found that HDV RNA level was the highest in patients with acute hepatitis (98%), whereas it was found at decreasing concentrations (74%, 74%, 63%) in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma, respectively (p=0.002). HBV DNA level was the lowest in patients with acute hepatitis (61%) as compared to the other groups (66%, 70%, 80%) (p=0.002), and consequently, they concluded that HDV was more dominant in the progression of disease (14). The results of our study revealed that HBV DNA levels were not statistically different between DA cirrhosis patients and patients with CHD. This result is similar to the result of the study conducted by Yamashiro et al. (13). However, HBV DNA levels in both groups were significantly lower than that in patients with chronic HBV infection. This outcome indicates not only suppressive character of HDV on HBV, but also supports the hypothesis that delta hepatitis is the primary agent responsible for progression of the disease (14).

In the present study, a correlation was found between serum HDV RNA and fibrosis stage. The findings indicated that HDV RNA positively correlated with necroinflammatory activity as well. It was also revealed that HDV RNA positively correlated with ALT level in CHD patients. In a study conducted by Braga et al. (15), mean HDV-RNA showed positive correlation with inflammatory activity and fibrosis stage. HDV viral load was correlated positively with serum levels of liver enzymes and inversely with platelet count. HBV viral load showed no correlation with any of the above-mentioned parameters. As a consequence, HDV may possibly play an important and direct role in the development of necroinflammatory activity and fibrosis. The results of our study confirm the findings in the study conducted by Braga et al. (15).

Higher necroinflammation score and advanced stage of fibrosis and accordingly more severe disease were observed in patients with CHD (9.30±2.89) than in patients with CHB (5.95±2.82) (p=0.001). In a study from Turkey conducted by Albayrak et al. (16),

12 patients with CHD underwent biopsy and the mean fibrosis stage was found to be 1.91±1.22 and mean necroinflammation score was found to be 8.92±1.83. While necroinflammation score was similar with that in our study, fibrosis stage was lower than in our study.

Conclusion

Our study revealed that age of onset of hepatitis and, accordingly, age of onset of related liver cirrhosis are lower in Turkey. ALT levels are not different between patients with CHD, DA cirrhosis and CHB. HBV DNA appears to be suppressed in patients with delta hepatitis as compared to patients with CHB. Histologically more severe findings were observed in patients with CHD and in HDV-positive cirrhotic patients. These results support the hypothesis that delta hepatitis together with hepatitis B plays a role as the dominant factor and accelerates disease progression.

Ethics

Ethics Committee Approval: Retrospective study.
Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

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Research Article

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Doi: 10.4274/vhd.2018.0004
Viral Hepatitis Journal 2018;24(2):53-56

HBsAg, Anti-HBs, Anti-HCV and HIV Seroprevalence in Hemodialysis Patients in Elazığ Province

Elazığ İlinde Hemodiyaliz Hastalarında HBsAg, Anti-HBs, Anti-HCV ve HIV Seroprevalansı

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ABSTRACT

Objectives: This study aimed to determine the rates of hepatitis B surface antigen (HBsAg), anti-HBs, anti-hepatitis C virus (HCV) and human immunodeficiency virus (HIV) seropositivity in hemodialysis patients in Elazığ province.

Materials and Methods: All patients receiving hemodialysis in Elazığ province were included in the study. Patients with HBsAg, anti-HBs, anti-HCV and HIV seropositivity were retrospectively evaluated using data between January 1, 2017 and December 12, 2017. Serological HBsAg, anti-HBs, anti-HCV and HIV values were tested. Patients' data regarding age, sex and dialysis duration were recorded.

Results: A total of 434 patients were included in the study. A hundred and sixty seven patients (38.5%) were female, and 267 (61.5%) were male. The mean age of the patients was 59.04 (range: 12-87) years. HBsAg, anti-HBs and anti-HCV positivity was detected in a total of 25 (5.8%) 341 (78.6%) and of 5 (1.2%) patients, respectively. HIV positivity was not found in any of the patients. When the relationship of seropositivity with dialysis durations and age groups was evaluated, no statistically significant difference was detected between the subgroups for HBsAg, anti-HBs and anti-HCV positivity rates.

Conclusion: The low rate detected for anti-HCV positivity in this study was related with the low prevalence of HCV in our province, decrease in the need for transfusion as a result of erythropoietin use, and strict and monitored application of infection control measures.

Keywords: Hemodialysis, hepatitis B, hepatitis C, human immunodeficiency virus, seroprevalence

ÖZ

Amaç: Bu çalışmanın amacı, Elazığ ilindeki hemodiyaliz hastalarında hepatit B yüzey antijeni (HBsAg), anti-HBs, anti-hepatit C virüsü (HCV) ve insan immün yetmezlik virüsü (HIV) seropozitiflik oranlarını belirlemektir.

Gereç ve Yöntemler: Elazığ'da hemodiyaliz alan tüm hastalar, bu çalışmaya dahil edildi. Hastaların HBsAg, anti-HBs, anti-HCV ve HIV seropozitiflik durumları 1 Ocak - 12 Aralık 2017 tarihleri arasındaki veriler kullanılarak retrospektif olarak incelendi. HBsAg, anti-HBs, anti-HCV ve HIV serolojik değerleri test edildi. Hastaların yaş, cinsiyet ve diyalize girme süreleri kaydedildi.

Bulgular: Çalışmaya toplam 434 hasta alındı. Bunların 167'si (%38,5) kadın, 267'si (%61,5) erkek idi. Hastaların yaşları 12 ile 87 arasında (ortalaması 59,04) idi. HBsAg pozitifliği toplam 25 (%5,8) hastada saptandı. Bu hastaların 20'si (%4,6) erkek ve 5'i (%1,2) kadın idi. Anti-HBs pozitifliği toplam 341 (%78,6) hastada saptandı. Anti-HCV, toplam 5 (%1,2) hastada pozitif saptandı. HIV poztitifliği hiçbir hastada saptanmadı. Diyalize girme süreleri ve yaş gruplarıyla ilgili seropozitiflik ilişkisi değerlendiğinde HBsAg, anti-HBs, anti-HCV pozitiflik oranında gruplar arasında anlamlı istatistiksel farklılık saptanmadı.

Sonuç: Bu çalışmada anti-HCV pozitifliği için tespit edilen düşük oran, ilimizdeki düşük HCV prevalansına, eritropoetin kullanımı sonucu transfüzyon ihtiyacının azalmasına ve enfeksiyon kontrol önlemlerinin sıkı ve takipli uygulanması ile ilişkili olduğunu düşünmekteyiz.

Anahtar Kelimeler: Hemodiyaliz, hepatit B, hepatit C, insan immün yetmezlik virüsü, seroprevalans

Eser Karlıdağ G, Küçüksu M, Demir M. HBsAg, Anti-HBs, Anti-HCV and HIV Seroprevalence in Hemodialysis Patients in Elazığ Province. Viral Hepat J. 2018;24:53-56.

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Introduction

Today, viral hepatitis is still an important health issue. The reasons increasing the risk of infection include more frequent blood transfusion in patients receiving hemodialysis (HD) with the diagnosis of chronic kidney disease compared to the general population, the necessity of vascular intervention with HD, advanced age, large number of patients receiving HD in the same place, increased sensitivity in patients due to weakened immune system, frequent hospitalization and surgical intervention. The prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection is known to be higher in special populations such as HD patients compared to the general population (1). Infection rates are higher in HD patients compared to continuous ambulatory peritoneal dialysis or home HD patients (2). Recent studies have reported that in our country, hepatitis B surface antigen (HbsAg)-positivity rate was 1-3% and anti-HCV positivity rate was around 1% in healthy individuals (1,3). It has been reported that HBsAg was found to be positive in 5.7% of HD patients, anti-HCV-positivity in 6.6%, and both HBsAg and anti-HCV positivity was found in small number of patients (1.1%) (4). This study mainly aimed to determine the rates of HBsAg, anti-HBs, anti-HCV and human immunodeficiency virus (HIV) seropositivity in HD patients in Elazığ province. Furthermore, with these data (as they are the initial data of this province), this study contributes to epidemiological data of our country and future studies aiming to determine the efficacy of infection control measures taken for HD patients.

Materials and Methods

All HD patients receiving treatment in four public hospitals and three private dialysis centers in Elazığ province were included in the study. Approval for the study was taken from Fırat University, Ethics Committee (decision no: 08, date: 01.02.2018). The patients' statuses of HBsAg, anti-HBs, anti-HCV and HIV seropositivity were retrospectively examined using data between January 1, 2017 and December 12, 2017. Patients' data regarding age, sex and dialysis duration were recorded individually. The patients were evaluated in five subgroups by dialysis duration as 0-12 months, 13-36 months, 37-72 months, 73-120 months, 121 months and over; and in eight subgroups by age as 10-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years, and 81 years and over.

Statistical Analysis

Serological HBsAg, anti-HBs, anti-HCV and HIV values were studied using Centaur XP Immunoassay system (Siemens, USA). HCV-RNA levels were measured by real-time polymerase chain reaction using Rotor-Gene Q instruments (Qiagen, Hilden, Germany). Data were assessed using SPSS package software v. 22.0. Pearson's chi-square test was used for the intergroup difference, and a p value of less than 0.05 was considered statistically significant.

Results

A total of 434 dialysis patients were included in the study. A hundred sixty seven patients (38.5%) were female, and 267 (61.5%) were male. The mean age of the patients was 59.04 years (range: 12-87), and the dialysis duration varied between 1 month and 240 months. HBsAg positivity was detected in a total of 25 (5.8%) patients. Twenty (4.6%) were male, and 5 (1.2%) were female. Anti-HBs positivity was detected in a total of 341 (78.6%) patients. When evaluated by sex, anti-HBs was positive in 145 (87%) females and 267 (73.4%) males. Anti-HCV was detected to be positive in a total of 5 (1.2%) patients (2 females and 3 males). All these patients had received antiviral therapy. HCV-RNA values were negative at 6 month after the completion of treatment. Their follow-up was ongoing. HIV-positivity was not detected in any of the study participants. Coexistence of HBsAg- and anti-HCV-positivity was not present in any of the study participants. When the relationship of seropositivity with dialysis durations and age groups was evaluated, no statistically significant difference was detected between the subgroups for HBsAg, anti-HBs and anti-HCV positivity rates ($p \geq 0.05$). HBsAg, anti-HBs and anti-HCV distribution by dialysis duration and age is shown in Tables 1 and 2.

Discussion

Hepatitis B and hepatitis C infection is still an important cause of morbidity and mortality in the world, and also one of the global public health issues. It has been reported that there were 248 million HBV carriers in the world, and annually, 600.000 individuals die from cirrhosis and hepatocellular carcinoma due to HBV infection. According to the World Health Organization data, it has been reported that approximately 450 million new cases occur each year and approximately 25% of these cases become chronic. These data suggest that this course will continue (5). Our country is in a region of moderate endemicity (2-7%) for HBV infection. According to the epidemiological data in our country, 3.5 million individuals are infected with HBV. HBV seroprevalence varies by region. In studies performed between 2008 and 2011 with the cooperation of the Association of Viral Hepatitis Control

Table 1. Hepatitis B surface antigen, anti-hepatitis B surface and anti-hepatitis C virus distribution by dialysis duration

		Dialysis duration					
		0-12 months	13-36 months	37-72 months	73-120 months	121-…months	Total
HBsAg-positive	n	3	5	6	8	3	25
	%	0.7%	1.2%	1.4%	1.8%	0.7%	5.8%
Anti-HBs-positive	n	27	106	86	65	57	341
	%	6.2%	24.4%	19.8%	15.0%	13.1%	78.6%
Anti-HCV-positive	n	0	0	2	2	1	5
	%	0.0%	0.0%	0.5%	0.5%	0.2%	1.2%

n: number of patiens, HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HBs: Hepatitis B surface

Table 2. Hepatitis B surface antigen, anti-hepatitis B surface and anti-hepatitis C virus distribution by patient age

		Age								
		10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-...	Total
HBsAg-positive	n	0	0	3	4	8	6	4	0	25
	%	0.0%	0.0%	0.7%	0.9%	1.8%	1.4%	0.9%	0.0%	5.8%
Anti-HBs-positive	n	4	13	24	43	76	83	78	20	341
	%	0.9%	3.0%	5.5%	9.9%	17.5%	19.1%	18.0%	4.6%	78.6%
Anti-HCV-positive	n	0	0	1	0	2	2	0	0	5
	%	0.0%	0.0%	0.2%	0.0%	0.5%	0.5%	0.0%	0.0%	1.2%

n: number of patiens, HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HBs: Hepatitis B surface

and Turkish Association for the Study of Liver (TASL), HBsAg prevalence was detected to be 2.4%, 1.9%, 3% and 2.7%, respectively by year. The highest prevalence was detected in the Southeastern Anatolia region with the rate of 4.1% and the lowest rate in Aegean region with 1.4% (1). More than 75% of HBV-infected patients in the general population around the world live Asia-Pacific countries. In a study involving Asia-Pacific countries, Johnson et al. (6) have reported an HBV seropositivity rate of 1.3-14.6%. In their multi-center, cross-sectional study involving seven countries, Burdick et al. (7) have detected a mean of 3% (0-6.6%) HBV seroprevalence in HD patients. In this study, they have reported that the HBV prevalence was 0-5% in 75% of dialysis units. According to the data of the Turkish Association of Nephrology in 2015, the prevalence of HBsAg-positivity has been reported to be 5.7% in chronic HD patients (1). Kaplan et al. (8) evaluated 3023 HD patients in Sivas province between 2002 and 2011, and detected a HBsAg seroprevalence rate of 3.5%. In studies performed in HD patients in various regions of our country, HBsAg-positivity was found to be 5.5% in Rize by Çiçek et al. (9), 6% in Istanbul by Alp (10), 3.6% in Hatay by Evirgen et al. (11), and 4.8% in Çanakkale by Arabacı and Olcaday (12). Due to immunosuppression in HD patients, the rate of achieving protective antibody response (10 mIU/mL) is low despite high-dose vaccination (40 g) (13). It has been reported that while response to 3 doses of vaccine in individuals with normal immune response was 90-95%, the mean rate of response to vaccination in HD patients was 64% (34-88%) (14). In some recent studies in our country, the vaccination response rate has been reported to be between 72.2% and 80% (9,11,12). In our study, we detected 5.5% HBsAg-positivity and 78.6% anti-HBs-positivity in HD patients. Our rates are comparable with the data in recent studies in our country. There are studies reporting the relationship of HBsAg-positivity with HD duration differently. While Franco et al. (15), from Italy, have demonstrated a relationship between HbsAg-positivity and HD duration, Balat et al. (16), from our country, detected no significant relationship. Our study did not find a statistically significant relationship between HD duration and HBsAg- and anti-HBs-positivity either. The mean prevalence of HCV infection is 2-3% in the world. Risk factors for HCV infection vary by region and population (17). In a country-wide study performed in Turkey by the TASL, the rate of anti-HCV positivity was found to be 0.95% in the general population (18). When global studies in HD patients were reviewed, a decrease was observed in anti-HCV positivity over time but an increase was also detected in some countries. HCV infection is especially important in dialysis patients because the prevalence is much higher than in the general population due to nosocomial transmission (9,19). In a meta-analysis in HD patients, being HCV carrier was found to increase the risk of mortality by 1.57-fold (20). Anti-HCV positivity rate varies by geographical region. In a multi-center study performed by Jadoul et al. (21) in Europe, it has been reported that anti-HCV prevalence decreased from 13.5% in 1991 to 6.8% in 2000, in Belgium, from 42% to 30% in France, from 16% to 9% in Switzerland, 28% to 16% in Italy, from 7% to 3% in the UK and from 26% to 15% in Hungary, and increased from 5% to 12% in Spain and from 42% to 44% in Poland. The authors have associated these decreases with the decrease in blood transfusion rates, thanks to erythropoietin use, and the increase in the sensitivity of anti-HCV tests. In our study, anti-HCV was found to be positive in 5 of 434 patients (1.2%). According to the data of the Turkish Association of Nephrology in 2015, the prevalence of anti-HCV-positivity in chronic HD patients has been reported to be 6.6% (1). In studies in our country, anti-HCV positivity was detected to be 28% by Alp (10), 4.1% by Temiz et al. (22), 9.5% by Evirgen et al. (11), 10% by Bozkurt et al. (23), 16% by Çiçek et al. (9), and 10.6% by Arabacı and Olcaday (12).

Conclusion

In our study, the rate of anti-HCV positivity was detected to be 1.2%. This value was lower than in the data published in recent years. We think that the low rate of anti-HCV positivity and the low prevalence of HCV infection in HD patients in our study are related with the low prevalence of HCV in our province, decrease in the need for transfusion as a result of erythropoietin use, and strict application of infection control measures. There was no anti-HIV-positive patient among HD patients in our study. While anti-HIV seroprevalence varies by geographical region, this result can be explained by the very low anti-HIV seroprevalence in our province. Our study involved all HD patients in the province. Our rates of HBsAg and anti-HBs in this study are comparable with the overall rates in the country. We think that the low rate detected for anti-HCV positivity in this study is related with the low prevalence of HCV in our province, decrease in the need for transfusion as a result of erythropoietin use, and application of infection control measures. Together with the hepatitis C treatment options providing cure in recent years, we think that the rate of HCV infection will also decrease in the country.

Ethics

Ethics Committee Approval: Approval for the study was taken from Fırat University Ethics Committee (decision no: 08, date: 01.02.2018).

Informed Consent: Informed consent is not required due to retrospective design of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

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Doi: 10.4274/vhd.2018.0012
Viral Hepatitis Journal 2018;24(2):57-60

The Role of New Viral Biomarkers in Chronic Hepatitis B: Ready to Use in the Clinical Practice?

Kronik Hepatit B'de Yeni Viral Göstergelerin Rolü: Klinik Uygulamada Kullanıma Hazır mı?

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ABSTRACT

Recent advances have been made to develop and improve the serologic and molecular virologic tools for the diagnosis and optimal management of chronic hepatitis B (CHB) infection. Several biomarkers associated with the natural course of chronic hepatitis B infection virus (HBV) and the efficacy of antiviral treatment have been defined. This article reviews the impact of hepatitis B surface antigen, hepatitis B core-related antigen and HBV RNA on the natural history, treatment response and outcomes of CHB infection.
Keywords: Hepatitis B surface antigen, hepatitis B core-related antigen, hepatitis B virus RNA

ÖZ

Son yıllarda kronik hepatit B (KHB) enfeksiyonunun tanısı ve optimal yönetimi için serolojik ve moleküler virolojik araçlar geliştirilmiştir. Kronik hepatit B virüsünün (HBV) doğal seyri ve antiviral tedavinin etkinliği ile ilişkili birçok viral gösterge tanımlanmıştır. Bu makalede, hepatit B yüzey antijeni, hepatit B kor-ilişkili antijen ve HBV RNA'nın KHB enfeksiyonunun doğal seyri, tedavi cevabı ve sonuçları üzerine etkisi derlenmiştir.
Anahtar Kelimeler: Hepatit B yüzey antijeni, hepatit B kor-ilişkili antijen, hepatit B virus RNA

Yapalı S. The Role of New Viral Biomarkers in Chronic Hepatitis B: Ready to Use in the Clinical Practice? Viral Hepat J. 2018;24:57-60.

Introduction

Chronic hepatitis B (CHB) infection affects over 350 million people in the world and it is responsible for more than 500.000 deaths annually (1). Cirrhosis and hepatocellular carcinoma (HCC) are the major complications of CHB infection. With the availability of potent antiviral agents, management of CHB patients improved. However, it is still difficult to predict the risk of liver disease progression and the risk of HCC in CHB infection. Furthermore, the clearance of covalently closed circular DNA (cccDNA) from the host genome and eradication of the virus cannot be achieved with the current treatments. The treatment recommendations of the professional liver societies are mainly based on the clinical status, serum hepatitis B virus (HBV) DNA, alanine aminotransferase (ALT) level, hepatitis B e antigen (HBeAg) status and liver histology (if available). High serum HBV DNA level is an independent predictor of HCC and an important determinant for the decision of treatment (2). With the recent advances in the molecular investigations, the role of new biomarkers in the natural history and during the treatment of CHB has been increasingly recognized. This article reviews the role of new biomarkers during the natural course and treatment of CHB infection, with a special emphasis on hepatitis B surface antigen (HBsAg) and hepatitis B core-related antigen (HBcrAg) levels and HBV-RNA quantification.

Hepatitis B Surface Antigen Quantification

Qualitative HBsAg is an important marker in the detection of HBV infection. The majority of HBsAg is secreted by subviral particles and to a lesser extent by infectious virions (3). HBsAg reflects the content of intrahepatic HBV DNA, cccDNA transcription and host immune response to HBV infection (4,5) The kinetics of

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HBsAg production are complex and show significant differences during the natural course of CHB and between HBV-genotypes. There is strong correlation of HBsAg with HBV replication only in the early phases of infection. The association between HBsAg and HBV DNA has been reported to be more prominent in HBV-genotype D, compared to HBV-genotype A. HBsAg levels were found to be related to HBV-reactivation in low viremic HBeAg-negative carriers (6). In a retrospective 8-year follow-up of HBeAg-negative CHB patients, HBsAg levels <100 IU/mL and HBV DNA <2.000 IU/mL were found to predict the inactive phase with a high chance of HBsAg loss. CHB patients with a HBV DNA level of 2.000-5.000 IU/mL who have an annual decline of HBsAg ≥0.5 log IU/mL have also been reported to have a high probability to become inactive carriers. HBsAg level has a good performance in identifying the phases of CHB during the natural course of the infection and can be helpful in determining the follow-up periods (7).

Serum HBsAg level correlates well with the cccDNA and intrahepatic HBV DNA and a is a strong predictor of response to pegylated-interferon (Peg-IFN) in HBeAg-positive patients. A reduction in HBsAg levels shows the induction of immune control. HBsAg level has been found to predict good response to Peg-IFN and lamivudine treatment better than HBV DNA (8). HBsAg level is an important predictor of response to Peg-IFN-α, however there may be genotypic differences (9,10). Quantification of HBsAg in HBeAg-positive patients may help in decision making regarding individualized treatment. In HBeAg-positive CHB patients, an HBsAg level of <1.500 IU/mL at week 12 predicts a high probability HBeAg seroconversion, while an HBsAg level of >20.000 IU/mL for HBV genotype B and C or no decline in HBsAg levels for HBV genotype A and D are associated with a very low rate of HBeAg seroconversion (9,10). The European Association for the Study of the Liver (EASL) recommends considering specific stopping rules according to HBsAg levels at week 12 of Peg-IFN treatment (11). In HBeAg-negative CHB patients, early serum HBsAg decline was found to be associated with sustained virological response in patients receiving Peg-IFN-α treatment (12). The combination of lack of decrease in HBsAg level and <2 log IU/mL decline at the 12th week of Peg-IFN treatment has 100% negative predictive value for treatment response and discontinuation of treatment is recommended by the EASL guideline (10).

Compared to Peg-IFN treatment, HBsAg decline during nucleoside/tide analogs (NA) therapy is much slower. The immune modulation by IFN results in a more rapid HBsAg decline. On the other hand, NAs inhibit only the reverse transcription of the pregenomic RNA but do not target the cccDNA directly and have a less pronounced effect on HBsAg secretory pathways (13,14). Furthermore, integrated HBV DNA in HBeAg-negative patients leads to production of HBsAg.

HBsAg levels in HBeAg-negative patients may be helpful to predict in which patient treatment can be stopped. A study by Hadziyannis et al. (15) showed that discontinuation of antiviral therapy led to sustained off-treatment HBV DNA suppression in 55% of patients and subsequent HBsAg loss in 39% of HBeAg-negative CHB patients who received adefovir treatment for 4-5 years. Lower HBsAg levels at the end of treatment were predictive for later HBsAg loss.

In a systematic review of 22 studies, an HBsAg level of <100 or <200 IU/mL at the end of therapy has been suggested to be a good indicator of sustained response (16). HBsAg levels have promising evidence for predicting in which patients treatment can be stopped, however, more data are needed to confirm the thresholds for discontinuation of treatment.

Hepatitis B Virus Core-related Antigen

HBcrAg is a novel biomarker of CHB infection, which measures serum levels of HBcAg, HBeAg and the empty particle (p22) (17). Quantification of HBcrAg is first developed in Japan by comparing the chemiluminescence signals generated by known concentration of recombinant pro-HBeAg (18). This assay (Fujirebio, Tokyo, Japan) is currently available with a lower limit of detection of 2.0 log U/mL, and a linear range of 3.0 log U/mL-7.0 log U/mL.

Serum HBcrAg level was found to correlate with serum HBV DNA, intrahepatic DNA and cccDNA levels (17). HBcrAg levels may show variation during the natural course of CHB infection. Studies in the European and Asian cohorts showed that HBcrAg levels were higher in HBeAg-positive CHB patients in comparison to HBeAg-negative patients (19,20). In an Asian cohort, it was found that HBcrAg levels were 8.54 log U/mL, and 7.92 log U/mL in the immune tolerant phase and in the immune clearance phase, respectively. Lower HBcrAg levels suggested a better immune control in HBeAg-positive patients. Among HBeAg-negative patients, HBcrAg levels were 2.60 log U/mL, and 4.92 log U/mL in inactive carriers and CHB patients, respectively. HBcrAg levels in HBeAg-negative patients with CHB showed a positive correlation with necroinflammatory activity and fibrosis (19). After HBsAg seroclearance, HBcrAg levels were found to be undetectable in 79% of patients, while 21% had median HBcrAg 2.7 log U/mL (19). HBcrAg levels were found to be associated with development of HCC in both treated and untreated patients (21,22). In a large cohort of 1031 CHB patients with a median 10-year follow-up, HBcrAg >2.9 log U/mL (HR, 5.05; 95% confidence interval, 2.40-10.63) was associated with an increased incidence of HCC (22).

HBcrAg may have an important role in predicting the clinical outcomes in patients on treatment. In their study, Wong et al. (23) reported that HBcrAg was detected in 101 (78%) of 130 samples with undetectable HBV DNA collected from NA-treated patients and there was a positive correlation between HBcrAg and cccDNA. As HBV DNA is undetectable in the majority of patients on treatment, HBcrAg levels may be considered as an indirect marker of cccDNA. The decline in HBcrAg has been found to be slower than in HBV DNA levels during NA treatment (24). The rationale is; NAs inhibit HBV DNA replication by the action on the reverse transcription but without elimination of cccDNA from the infected hepatocyte. In some Asian studies, the decline of HBcrAg was found to correlate with the decline of intrahepatic cccDNA in patients receiving entecavir treatment (23,25,26).

In a study of 46 patients treated with Peg-IFN, a baseline HBcrAg level of >8 log U/mL was reported to have low probability of HBeAg seroconversion (>94.4% negative predictive value) and suppression of HBV DNA at 12 weeks (27). Furthermore, changes in HBcrAg levels may be helpful in predicting clinical outcomes during treatment. In a study of 58 HBeAg-positive CHB patients treated with Peg-IFN, the HBcrAg at week 12 of therapy was

found to be predictive of HBeAg seroconversion at 24 weeks after completion of therapy (28).

The role of HBcrAg for predicting HBsAg loss was examined in a study of 62 HBeAg-negative CHB patients receiving Peg-IFN alone or in combination with tenofovir, the chance of HBsAg loss was higher in patients with baseline HBcrAg <3.7 log U/mL (29).

The majority of HBeAg-negative CHB patients remain on treatment until HBsAg loss is achieved. There are many attempts to determine the predictors of relapse after discontinuation of treatment. The decision for discontinuation of treatment can be determined by viral serological markers, serum HBV DNA, ALT and more recently, HBsAg levels. HBcrAg levels may provide prognostic information for the decision of treatment discontinuation. In studies performed in Japan, a high end-of-treatment HBcrAg level was shown to predict relapse after discontinuation of NA therapy (30,31,32,33). In a study of 113 patients receiving NA treatment (lamivudin: 32, entecavir: 81), end-of-treatment HBcrAg level >3.7 log IU/mL predicted virological relapse within 1 year of NA discontinuation (33). The Japanese Society of Hepatology guidelines have recently recommended the use of an HBsAg level of <1.9 log U/mL and an HBcrAg level of <3.0 log U/mL to identify patients at low risk of relapse (34). However, there is a need to examine the performance of these criteria in different populations.

Recently, HBcrAg positivity has been found to be a significant risk factor for HBV reactivation in HBsAg-negative, anti-HBc-positive patients undergoing high-risk immunosuppressive therapy (especially rituximab-containing chemotherapy), and to have potential to identify patients who would most benefit from prophylactic antiviral treatment (35).

The use of HBcrAg will most probably lead to progress in the management of CHB. However, most of the studies are performed in Japan and Asian countries, and these data need to be confirmed in the Western populations.

Hepatitis B Virus RNA Quantification

During HBV replication, pregenomic RNAs are encapsidated into HBV core particles in the cytoplasm, and all pregenomic RNAs are reverse transcribed into plus stranded genomic DNA in the core particle (36). HBV RNA has also been detected in the serum of CHB patients and found to strongly correlate with HBV DNA levels (36). Studies have reported decreased HBV RNA levels in patients receiving NA and the combination of Peg-IFN and NA (37,38). The decrease in HBV RNA levels was predictive for HBeAg seroconversion suggesting a better role of HBV RNA ± HBV DNA for treatment monitoring (37,38).

Conclusion

HBsAg, HBcrAg and HBV RNA quantification provides new perspectives in understanding HBV virology and immunopathogenesis. The implementation of HBsAg quantification has already been integrated into European treatment guidelines. The use of HBcrAg seems to be in the pipeline, however, the results need to be validated in other populations with different ethnic and genotypic characteristics. There is a growing body of evidence for the impact of HBV RNA in patients receiving treatment. In future, the use of new biomarkers may guide the clinicians to predict the natural course, treatment response and the outcome of CHB, adapting individualized treatment approaches.

Ethics

Peer-review: Internally peer-reviewed.

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

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Doi: 10.4274/vhd.2018.0001
Viral Hepatitis Journal 2018;24(2):61-64

A Case of Hepatitis B Reactivation with Acute Flare Three Months After Tenofovir Prophylaxis Withdrawal in a Allogenic Hematopoietic Stem Cell Transplantation Patient

Bir Allojenik Hematopoietik Kök Hücre Nakli Hastasında, Tenofovir Profilaksisinin Bırakılmasından Üç Ay Sonra Akut Alevlenme ile Hepatit B Reaktivasyon Olgusu

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ABSTRACT

Hepatitis B virus (HBV) infection is a major health problem worldwide. HBV reactivation is associated with high mortality rates in hematopoietic stem cell transplantation (HSCT) and, prophylactic antiviral treatment is suggested to prevent this phenomenon. However, the duration of antiviral treatment in HSCT patients is not fully defined and the time of immune recovery is considered the best parameter for a drug to be safely interrupted. We aimed to present a case of hepatitis B reactivation after cessation of one-year prophylactic tenofovir treatment in a anti-hepatitis B core immunoglobulin G-positive patient who received allogenic HSCT treatment for chronic lymphocytic leukemia.
Keywords: Hepatitis B reactivation, tenofovir, hematopoietic stem cell transplantation

ÖZ

Hepatit B virüs (HBV) enfeksiyonu dünya çapında önemli bir sağlık sorunudur. Hematopoietik kök hücre transplantasyonunda (HSCT) HBV reaktivasyonu yüksek mortalite oranları ile ilişkilidir ve bu durumun önlenmesi için profilaktik antiviral tedavi önerilmektedir. Bununla birlikte, HSCT hastalarında verilecek antiviral tedavinin süresi tam olarak tanımlanmamıştır ve antiviral tedavinin sonlandırılmasında bağışıklık kazanım zamanı en güvenilir parametre olarak kabul edilmektedir. Biz burada, kronik lenfositik lösemi tanısıyla allojenik HSCT tedavisi uygulanan anti-hepatit B core immünoglobulin G pozitif bir hastada transplant sonrası verilen bir yıl profilaktik tenofovir tedavisinin kesilmesi sonrasında ortaya çıkan bir hepatit B reaktivasyonu olgusunu sunmayı amaçladık.
Anahtar Kelimeler: Hepatit B reaktivasyonu, tenofovir, hematopoietik kök hücre transplantasyonu

Toka B, Eminler AT, Aslan FG, Köksal AŞ, Altındiş M. A Case of Hepatitis B Reactivation with Acute Flare Three Months After Tenofovir Prophylaxis Withdrawal in A Allogenic Hematopoietic Stem Cell Transplantation Patient. Viral Hepat J. 2018;24:61-64.

Introduction

The natural course of hepatitis B virus (HBV) infection is determined through the interaction between viral replication and the host immune response. HBV reactivation is defined as elevation of the viral DNA level or alteration of the hepatitis B surface antigen (HBsAg) seroconversion status. In HBsAg carriers, it is characterised by either increase in HBV DNA level by >1 log (10 fold) or HBV DNA turning positive. Other than this, in HBsAg- and antibody to hepatitis B core antigen (anti-HBc)+ patients, reverse seroconversion of HBsAg from negative to positive is defined as reactivation (reappearance of HBsAg with or without increased liver enzymes) (1,2). Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) are considered high risk for HBV reactivation (3), with a mortality rate of up to 40%. Third-generation antiviral drugs (entecavir or tenofovir) are recommended for patients with HBsAg or anti-HBc immunoglobulin (Ig) G-positive haematologic patients regardless of

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HBV DNA levels (4,5). Antiviral therapy initiated simultaneously with or prior to immunosuppressive therapy can reduce the risk of HBV reactivation. Many studies have evaluated the efficacy of prophylactic therapy (6,7); however, the duration of antiviral treatment in HSCT patients is not fully defined. We aimed to present a case of hepatitis B reactivation after cessation of one-year prophylactic tenofovir treatment in an anti-HBc IgG-positive patient who received allogenic HSCT treatment for chronic lymphocytic leukemia.

Case

A 64-year-old male patient was admitted to our clinic with the complaints of fatigue, nausea, vomiting, and jaundice. His complaints began 3 days ago and gradually increased. Anti-HBc IgG positivity was detected 16 months ago with the screening tests performed before the immunosuppressive treatment. The patient was treated with 2 cycles of rituximab and then allogenic HSCT was performed for chronic lymphocytic leukemia. He was administered cyclosporin 5 mg/kg for six months after HSCT, then the dose was reduced and stopped at the end of the one-year treatment. During the rituximab period, he was administered prophylactic tenofovir 245 mg/day and for one year following HSCT treatment. Tenofovir treatment was stopped three months ago (one year after HSCT). He did not have any chronic diseases and there was no any liver disease in his family history. On physical examination, his sclera and the skin were icteric. His laboratory findings were as follows: alanine aminotransferase (ALT): 1365 U/L, aspartate aminotransferase (AST): 1066 U/L, alkaline phosphatase (ALP): 276 U/L, gamma-glutamyl transferase (GGT): 108 U/L, total biluribin: 18.44 mg/dL, direct biluribin: 9.46 mg/dL, international normalized ratio (INR): 1.40, albumin: 4.1 g/dL, white blood cell count: 5.690/uL, hemoglobin level: 15 g/dL, and platelet count: 67.000/uL. Alpha feto-protein level was not measured. The kidney function tests and electrolyte levels were normal. HBsAg, anti-HBc IgM, anti-HBc IgG, and anti- hepatitis B e (HBe) were found to be positive whereas HBe antigen (HBeAg) and delta antigen were found negative. HBV DNA level was 486.336.116 IU/mL. Other serological markers of viral infection (such as Epstein-Barr virus, cytomegalovirus, herpes simplex virus, hepatitis A, C, and E viruses) were all negative. Abdominal ultrasonography showed normal liver.

When the patient's tests performed prior to tenofovir withdrawal were investigated, it was seen that anti-HBc IgG was positive and HBsAg was negative. Liver function tests were normal when he received chemotherapy and one year post-HSCT. The treatment of tenofovir 245 mg was started again with the diagnosis of hepatitis B reactivation. After 2 months of tenofovir treatment his laboratory findings were found to be: ALT: 48 U/L, AST: 76 U/L, ALP: 230 U/L, GGT: 305 U/L, total bilirubin: 4.19 mg/dL, direct bilirubin: 1.60 mg/dL, INR: 1.12, albumin: 3.2 g/dL, and HBV DNA 17.932 IU/mL (Table 1).

Informed consent for publication was obtained from the patient.

Table 1. Laboratory findings

	Before HSCT	Before tenofovir cessation	3 months after tenofovir cessation, acute HBV flare	After 2 months of tenofovir treatment
ALT U/L	26	30	1365	48
AST U/L	30	18	1066	76
Total biluribin mg/dL	0.45	0.86	18.44	4.19
INR	1	0.98	1.40	1.21
HBsAg	-	-	+	+
Anti-HBc IgG	+	+	+	+
Anti-HBs	-	-	-	-
HBe Ag	-	-	-	-
Anti-HBe	+	+	+	+
Anti-HBc IgM	-		+	
HBV DNA IU/mL	-	-	486.336.116	17.932

HSCT: Hematopoietic stem cell transplantation, HBV: Hepatitis B virus, ALT: Alanine aminotransaminase, AST: Aspartate aminotransferase, INR: International normalized ratio, HBsAg: Hepatitis B surface antigen, HBc: Hepatitis B core antigen, IgG: Immunoglobulin G, HBs: Hepatitis B surface, HBe: Hepatitis B e, IgM: Immunoglobulin M

Discussion

Patients with malignancy, autoimmune diseases or HSCT with serologic evidence of HBV infection (HBsAg or anti-HBc IgG-positive) are at risk for HBV reactivation if they receive immunosuppressive therapy. Reactivation of HBV infection in the setting of chemotherapy and immunosuppression is associated with significant morbidity and mortality (8).

Hepatitis B reactivation appears to correlate with the level of immunosuppressive potency of the chemotherapy administered as well as with the use of concomitant steroids (9). The rate of HBV reactivation has been reported to be as high as 70% among HBsAg-positive individuals receiving HSCT or anti CD20 treatment (2). The risk of HBV reactivation depends on many factors including the virological and serological status of the infected patient, immunosuppressive potency of the therapy received, underlying disease, male sex, younger age, HBsAg, HBeAg and/or HBV DNA positivity at the baseline (10). HBsAg-positive patients are more likely to experience HBV reactivation than HBsAg-negative and anti-HBc-positive patients (11). Although the risk is lower, isolated anti-Hbc-positive patients still carry a definite risk of reactivation (12). However, there is limited evidence that the presence of anti-HBs is protective against HBV reactivation. An earlier study on 29 lymphoma patients reported no HBV reactivation in any of the patients (0/10) whose anti-HBs titer was higher than 100 IU/mL and low anti-HBs titer was independently associated with HBV reactivation (13). In patients receiving HSCT, anti-HBs titer of the donor was associated with a reduction in HBV reactivation risk. These findings have not yet been confirmed (14). Severe hepatitis can develop in up to 30-50 percent of patients with HBV reactivation (2,15), therefore, antiviral therapy should be initiated in these patients.

According to the American Gastroenterological Association guidelines, high-risk patients should be treated with prophylactic antiviral therapy prior to or concurrently with the immunosuppressive treatment. Moderate-risk patients can be

treated with antiviral prophylaxis or monitored closely (16). Antiviral prophylaxis is not recommended for low-risk patients and there are no recommendations about monitoring in untreated patients. The European Association for the Study of the Liver (EASL) recommends antiviral prophylaxis for HBsAg-positive patients and for HBsAg-negative/anti-HBc-positive patients receiving rituximab, bone marrow or stem cell transplantation (17). Regarding HBsAg-positive patients, most treatment guidelines such as the American Association for the Study of Liver Diseases (initiation of antivirals at the onset of immunosupression), and the Asian Pacific Association for the Study of the Liver guidelines (initiation of antivirals one week prior to chemotherapy) recommend prophylactic treatment (18,19).

Seto et al. (20) published a prospective study investigating the course of 62 HBsAg-negative, anti-HBc-positive HSCT recipients. The 2-year cumulative HBV DNA detectability rate was 40.8%, occurring at a median of 44 weeks, and entecavir successfully suppressed HBV DNA to undetectable levels, with no cases developing biochemical hepatitis.

Entecavir or tenofovir can be used in the treatment of HBV reactivation (21). The success rate of early antiviral therapy is high in patients with acute flare (22). The EASL recommends ALT and HBV DNA testing every 1-3 months during monitoring and treatment upon any evidence of HBV reactivation (23).

Patients with positive HBV serologic markers receiving immunosuppressive therapy or HSCT are at high risk for reactivation. As seen in our case, 12 months of prophylaxis treatment may not be sufficient for patients undergoing allogeneic HSCT. Current guidelines recommend that the duration of prophylaxis after HSCT and high-risk immunosuppressive therapy should be 12-18 months (24). However, the risk of HBV reactivation in HSCT can persist for several years after transplantation due to the long delays in the immune reconstitution.

Ethics

Informed Consent: Informed consent for publication was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.T., A.T.E., M.A., Design: B.T., F.G.A., Data Collection or Processing: B.T., A.T.E., F.G.A., M.A., A.Ş.K., Analysis or Interpretation: B.T., A.T.E., A.Ş.K., Literature Search: B.T., A.T.E., F.G.A., Writing: Bilal Toka, A.T.E., F.G.A., M.A., A.Ş.K.

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

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

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