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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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INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

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

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

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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.

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

The 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).

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

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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;

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

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

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

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

Conclusion: The conclusion of the study should be highlighted.

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

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

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

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).

Letters to the Editor

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

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• 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.

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

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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"

• All figures (with legends) and tables (with titles) cited.

• "Copyright Form" signed by all authors.

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Review

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Viral Hepatitis Journal 2023;29(3):90-94

Drug Resistance to HCV in Direct-Acting Antiviral Treatments

Doğrudan Etkili Antiviral Tedavilerde HCV İlaç Direnci

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ABSTRACT

Approved treatment protocols for hepatitis C virus (HCV) include direct-acting antiviral drugs (DAA), which consist of NS3 protease inhibitors (PI), NS5A replication complex inhibitors, and NS5B polymerase nucleoside and non-nucleoside inhibitors (NNI). First-generation DAAs are effective in specific genotypes (GT), such as NS5AIs (dasabuvir), PIs (asunaprevir, grazoprevir, paritaprevir/r, and simeprevir), and NNIs (ledipasvir, ombitasvir, and elbasvir). Second-generation DAAs are "pan-genotypic" and include NS5AIs (velpatasvir and pibrentasvir), PIs (voxilaprevir and glecaprevir), and an NSBNI (sofosbuvir). DAAs can potentially cure people with hepatitis C. However, although generally well tolerated, DAAs have not been observed to produce sustained virological response in some patients. Resistance-associated amino acid changes (RAS), which can lead to treatment failure, may be the reason for this. The RASs can occur naturally or during treatment and are influenced by various factors such as the treatment plan, HCV-GT/subtype, and endemic characteristics. While there are no standardized tests for investigating HCV-RAS, Sanger dideoxynucleotide sequencing-based approaches are generally reliable, even though their sensitivities range from 10% to 25%. However, new generation sequencing techniques are more sensitive and can detect variants with a prevalence of 1%, despite some ongoing debate about the clinical significance of variants at this level.

Keywords: Hepatitis C, HCV, direct-acting antiviral, drug resistance

ÖZ

Hepatit C virüs (HCV) için onaylanmış tedavi protokolleri, NS3 proteaz inhibitörleri (PI), NS5A replikasyon kompleksi inhibitörleri ve NS5B polimeraz nükleozid ve non-nükleozid inhibitörlerden (NII) oluşan direkt etkili antiviral ilaçları (DAA) içerir. Birinci nesil DAA'lar, NS5AI'lar (dasabuvir), PI'lar (asunaprevir, grazoprevir, paritaprevir/r ve simeprevir) ve NNI'lar (ledipasvir, ombitasvir ve elbasvir) gibi spesifik genotiplerde (GT) etkilidir. İkinci nesil DAA'lar "pan-genotipiktir" ve NS5AI'ları (velpatasvir ve pibrentasvir), PI'ları (voksilaprevir ve glekaprevir) ve bir NSBNI'yı (sofosbuvir) içerir. DAA'lar, hepatit C'li hastaları potansiyel olarak tedavi edebilir. Ancak, genellikle iyi tolere edilmelerine rağmen, DAA'ların bazı hastalarda kalıcı virolojik yanıt sağlamadığı gözlemlenmiştir. Tedavi başarısızlığına yol açabilen dirençle ilişkili aminoasit değişiklikleri (RAS), bunun nedeni olabilir. RAS'ler doğal olarak veya tedavi sırasında ortaya çıkabilir ve tedavi planı, HCV-GT/alt tipleri ve endemik özellikler gibi çeşitli faktörlerden etkilenir. HCV-RAS'leri araştırmak için standartlaştırılmış testler bulunmamakla birlikte, duyarlılıkları %10 ila %25 arasında değişse de Sanger dideoksinükleotid sekanslama genellikle güvenilirdir. Bununla birlikte, yeni nesil sıralama teknikleri daha hassastır ve klinik önemi hakkında devam eden bazı tartışmalara rağmen, %1'lik prevalansa sahip varyantları saptayabilir.

Anahtar Kelimeler: Hepatit C, HCV, direkt-etkili antiviral, ilaç direnci

Cite this article as: Sayan M. Drug Resistance to HCV in Direct-Acting Antiviral Treatments. Viral Hepatitis Journal 2023;29(3):90-94

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Introduction

According to the World Health Organization (WHO), approximately 58 million individuals across the globe are currently living with hepatitis C infection. Even children and adolescents are not spared, as an estimated 3.2 million people are affected by this infection. Shockingly, approximately 79% of these cases have not been diagnosed, and only 13% have received treatment. Although hepatitis C virus (HCV) is still prevalent among specific populations, such as intravenous drug users (IVDUs) and homosexual men, there is good news. Direct-acting antiviral drugs (DAAs) can potentially cure people with hepatitis C. However, limited access to diagnosis and treatment worldwide is still a concern (1,2).

Viral Fitness

HCV is a type of RNA virus with a single strand that falls under the hepacivirus genus of the Flaviviridae family (3). The genomic RNA of HCV is ~9.6 kb, and the RNA-coding polyprotein precursor is ~3000 amino acids in size. The genome organization of HCV is shown in Figure 1. HCV has a remarkably high daily replication rate of 10^{12} virions. The virus's NS5B polymerase activity, which is responsible for RNA-dependent RNA polymerase, has a significant error rate of 10^{-3} to 10^{-5} per base pair copied and lacks error correction capabilities (3,4). This error rate generates mutant variants during viral replication, resulting in the replicative HCV population's significantly increased genetic diversity. Research suggests that this genetic diversity may lead to speciation associated with resistance to therapies (5).

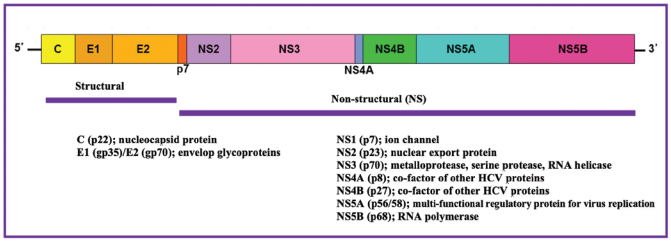

Figure 1. Genome organization of HCV. Genomic RNA is ~9.6 kb, and RNA encoding polyprotein precursor is ~3000 amino acids (6-8)
HCV: Hepatitis C virus

AASLD/IDSA 2023 Guideline

Guidelines for diagnosing, treating, and managing HCV infection were released for the first time in 2013 by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) (www.aasld.org). These guidelines aimed to provide clinicians with unbiased and evidence-based recommendations. Second-generation DAAs have proven to be highly effective in eliminating hepatitis C, which is critical for achieving the WHO-HCV elimination targets. Although generally well tolerated, some patients may not achieve sustained virologic response (SVR). This can occur because of resistance-associated substitutions (RAS), which can cause treatment failure (9,10). Approved DAAs for hepatitis C treatment according to first- and second-generation specifications by the European Medicines Agency and the U.S. The Food and Drug Administration are shown in Table 1. However, the preferred treatment/retreatment regimens for HCV-infected patients according to the AASLD-IDSA 2023 update guide are shown in Table 2.

Table 1. Direct-acting antivirals approved for hepatitis C treatment according to first- and second-generation specifications (5,11,12)

HCV drug class target	Direct-acting antiviral	
	First generation	Second generation
NS3PIs	Simeprevir, grazoprevir, asunaprevir, and paritaprevir/r	Glecaprevir, voxilaprevir
NS5AIs	Daclatasvir, ledipasvir, elbasvir, and ombitasvir	Pibrentasvir, velpatasvir
NS5BNI/NNI	Dasabuvir	Sofosbuvir

HCV: Hepatitis C virus, NS3PIs: NS3 protease inhibitors, NS5AIs: NS5A replication complex inhibitors, NS5B NI/NNI: NS5B polymerase nucleoside and non-nucleoside inhibitors

Table 2. Preferred treatment/retreatment regimens for HCV-infected patients in the AASLD-IDSA guide 2023 update (13)

HCV-DAA target	DAA treatment regimen	Brand name	Manufacturer	Country
NS3PIs + NS5AIs containing	Grazoprevir/elbasvir	Zepatier	MSD	Rahway, NJ, USA
	Glecaprevir/pibrentasvir	Maviret	abbVie	North Chicago, IL, USA
NS5BNIs containing	Ledipasvir/sofosbuvir	Harvoni	Gilead	San Dimas, CA, USA
	Velpatasvir/sofosbuvir	Epclusa	Gilead	San Dimas, CA, USA
	Voxilaprevir/velpatasvir/sofosbuvir	Vosevi	Gilead	San Dimas, CA, USA

HCV: Hepatitis C virus, AASLD: American Association for the Study of Liver Diseases, IDSA: Infectious Diseases Society of America, DAA: Direct-acting antiviral, NS3PIs: NS3 protease inhibitors, NS5AIs: NS5A replication complex inhibitors, NS5BNIs: NS5B polymerase nucleoside inhibitors

Direct-Acting Antivirals

The treatment of hepatitis C has progressed significantly because of the development and authorization of DAA medications. More than 95% of cases are cured when a patient achieves SVR. Approved treatment plans for HCV now include DAAs, which consist of NS3 protease inhibitors (PIs), NS5A replication complex inhibitors (NS5AIs), and NS5B polymerase nucleoside (NS5BNIs) and non-nucleoside (NS5BNNIs) inhibitors. First-generation DAAs are effective in specific genotypes (GT), such as NS5AIs (dasabuvir), PIs (asunaprevir, grazoprevir, paritaprevir/r, and simeprevir), and NNIs (ledipasvir, ombitasvir, and elbasvir). Second-generation DAAs are "pan-genotypic" and include NS5AIs (velpatasvir and pibrentasvir), PIs (voxilaprevir and glecaprevir), and an NSBNI (sofosbuvir) (Table 1) (https://www.hcvguidelines.org/).

Resistance-Associated Substitutions

It is crucial to consider that RASs may hinder the success of DAA treatments for hepatitis C. Depending on the current DAA and HCV-GTs, Table 3 lists the most common RASs found in the NS3, NS5A, and NS5B drug target areas. These RASs can occur naturally or during treatment and are influenced by various factors such as the treatment plan, HCV-GT/subtype, and endemic characteristics (14).

Conducting HCV resistance analysis has become increasingly crucial for improving the effectiveness of treatment and avoiding the reemergence of HCV-resistant variants for DAAs. Although there are no standardized tests for investigating HCV-RAS, Sanger dideoxynucleotide sequencing-based approaches are generally reliable, even though their sensitivities range from 10% to 25.0%. However, new generation sequencing (NGS) techniques are more sensitive and can detect variants with a prevalence of 1%, despite some ongoing debate about the clinical significance of variants at

Table 3. Resistance-associated substitutions are natural or acquired after a failure to a DAA regimen in the HCV-NS3, NS5A, and NS5B drug class targets according to the latest-generation DAA and HCV genotype (5,11,12,15-17)

HCV drug class target	Direct-acting antiviral	HCV-RAS patterns associated with treatment failure considering HCV genotypes					
		GT1a/b	GT2	GT3	GT4	GT5	GT6
NS3	Simeprevir	V36M, Q80K/R, S122R/T, R155K/G/T, D168A/E/F/H/N/V/T	NA	NA	V36M, Q80K/R, S122R/T, R155K/G/T, D168A/E/F/H/N/V/T	NA	NA
	Grazoprevir	V36L/M, Y56F/H, Q80K/L, R155G/I/K/L/Q/S/T, A156G/M/V/T, V158A, D168A/C/E/G/H/K/N/V/Y	NA	NA	A156S/T, D168A/C/E/G/K/N/V/Y	NA	D168A/C/E/G/K/N/V/Y
	Asunaprevir	Q80K/L, D168A/E/H/Q/T/V/Y	NA	NA	NA	NA	NA
	Paritaprevir/r	Y56H, R155K, D168A/C/E/G/K/N/V/Y	NA	NA	Y56H, D168A/C/E/G/K/N/V/Y	NA	NA
	Glecaprevir	V36M, Y56H/N, Q80K/R, S122G, R155T, A156G/T/V, and Q168A/K/L/R/V	No RASs	V36M, Y56H/N, Q80K/R, R155T, A156G/T/V, and Q168A/K/L/R	ND	ND	ND
	Voxilaprevir	Q80K, A156L/T/V	No RASs	No RASs	A156S	No RASs	ND
NS5A	Daclatasvir	M28A/T, Q30E/H/K/R, L31IF/M/V, R30H, H58D, and Y93C/H/I/N/R	ND	A30K, L31I, Y93H	L28M/V, L30H/R/S, Y93C/H	ND	ND
	Ledipasvir	K24R, L28M, M28A/T/V, Q30E/H/K/R/Y, L31F/I/M/V, S38F, H58D, A92T, and Y93C/F/H/N	NA	No RASs	L28M, L30H/R, M31L/V, T/P58L, and Y93C/H/S	NA	NA
	Elbasvir	M28A/G/S/T, Q30D/E/G/H/K/R/Y, R30H, L31F/I/M/V, H58D, and Y93C/H/N/S	NA	NA	L28M/S, L30H/R, M31L/V, P58D, and Y93C	NA	NA
	Ombitasvir	L28M, M28T/V, Q30E/H/K/L/R/Y, R30Q, L31F/M/V, H58D, Y93C/F/H/L/N/S	NA	NA	L28S/V, L30R, M31L/V, Y93H	NA	NA
	Pibrentasvir	K24R, M28A/G, Q30K/R, L31F/M, P32del, H58D, and Y93H/N	F28C, L31M	S24F, M28G/K, A30G/K, L31F/I/M, P58T, and Y93H	ND	ND	ND
	Velpatasvir	M28T/V, Q30E/H/K/L/R, L31I/M/V, Y93C/H/L/N/R/S/W/T	L31I/M/V, Y93H	A30K/V, L31M/P/V, E92K, Y93H/N/R	ND	ND	ND
NS5B	Dasabuvir	C316H//N/Y, M414I/T/V, Y448C/H, A553T/V, G554S, S556G/N, G558R, D559N/G	NA	NA	NA	NA	NA
	Sofosbuvir	L159F ± C316N or L320F, L159F + V321A, S282G/R/T	S282T	L159F ± C316N or L320F, L159F + V321A, and S282R/T	S282C/T	S282T	S282T

DAA: Direct-acting antiviral, HCV: Hepatitis C virus, NS: Non-structural, RAS: Resistance-associated amino acid substitutions, GT: Genotype, NA: Not applicable, ND: No data

this level. There is still some controversy regarding the therapeutic importance of mutations below 15% in patient samples (18).

Aspects for Clinics

For pan-genotypic DAA regimens, baseline RAS resistance testing is generally not recommended for velpatasvir/sofosbuvir and glecaprevir/pibrentasvir. It is worth mentioning that NS3 RASs can result in Q80K in up to 40% of patients with HCV-genotype 1a (GT1a), whereas NS5A RASs may be present in 5% to 15% of patients. For some cases, conducting a baseline RAS resistance analysis could be advantageous in identifying the best DAA treatment for patients with HCV-GT3 infections who have not been treated before. In hepatitis C, drug resistance is typically linked to RASs emerging due to DAA suppression. Notably, RASs in HCV can revert to their wild type, which can take several months for the NS3 gene region and years for the NS5A gene region (17,19,20).

The guidelines for treating GT1a infection have been updated in the IDSA 2023 guidelines, and the recommended treatment regimen has been revised. The previous suggestion of using elbasvir/grazoprevir has been substituted with a different treatment plan because it is necessary to conduct a baseline RAS analysis. The updated guidelines now suggest NS5A RAS analysis for treating HCV-GT3 infection with compensated cirrhosis and for initial treatment in adult patients infected with HCV-GT1-6. It is recommended to add ribavirin by weight or follow another recommended course of therapy if the natural prevalence of RAS is greater than 5% and baseline NS5A RAS Y93H is present (13).

Research has demonstrated that certain RASs can have an impact on SVR rates in hepatitis C, which can make it challenging to identify treatment options for patients who have already undergone treatment (17,21). Although newer and more effective DAA regimens are available for first- or second-line treatments, obtaining access to them can pose a challenge (22). Studies of in vivo infectious cDNA clones of HCV-GT3 in human hepatoma cells (Huh7.5) have shown that adaptation to NS5A drug resistance is also possible in pan-genotypic HCV-DAA regimens (23,24). A recently published real-life-based study focused on the NS3 and NS5B resistance of Asian HCV-GT3. Phylogenetic analyses indicate that GT3a is of Asian origin. GT3a has been observed to be similar to Asia in IVDUs in Europe (25). The rates of SVR with DAAs are very high; early treatment can reduce chronic hepatitis C complications and disease transmission. Considering this information, a more comprehensive understanding of RASs is essential to tailor first-line therapy and determine the most appropriate course of action for second-line therapy (26,27).

SHARED Initiative

The treatment of hepatitis C involves a range of genetic types and subtypes, making it challenging to obtain information about treatment resistance from local, regional, and short-term clinical trials. However, these studies have limited potential for generalized findings and are not commonly found in real-life cohorts. Although second-generation potent DAA treatment regimens can counter the adverse effects of RASs, the causes of virologic failure remain unclear. Studies addressing DAA resistance in hepatitis C lack standardization of analytical techniques and no clear definition of RASs. Despite the International Hepatitis C Treatment Guidelines recommending resistance testing for specific regimens or patient groups, the evaluation of drug resistance test results is not standardized. In response to this challenge, the Surveillance of Hepatitis C Antiviral Resistance, Epidemiology, and Methodologies (SHARED) is a global initiative that aims to develop, apply, and share HCV genomic data, methods, software, and technologies to better understand and prevent HCV drug resistance (28). The SHARED international collaboration is a formidable entity comprising physicians, virologists, and researchers from 22 countries and over 110 medical facilities and laboratories. This powerhouse possesses a vast database of HCV sequences, comprehensive patient information, disease characteristics, treatment histories, and clinical outcomes. The thorough and diverse nature of the data allows for unparalleled analysis. It provides unparalleled insights into HCV-DAA resistance on a global scale - insight that individual studies cannot match (5).

Conclusion

In conclusion, drug resistance caused by RAS to DAA medications can lead to an inadequate response to antiviral therapy and relapse in HCV-infected patients. We should be aware that HCV has high genetic variability, and RASs may lead to future failure of currently available DAA treatments. Therefore, monitoring drug resistance may be essential for pan-genotypic HCV-DAA regimens. RAS can occur naturally or be selected during therapy. To determine the most appropriate DAA treatment, it is crucial to identify the HCV-GT/subtype and detect pre-existing RAS. The analysis can be performed using either Sanger sequencing or NGS sequencing.

Ethics

Peer-review: Externally peer-reviewed.

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Research Article

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Clinical Efficacy and Safety of Direct-Acting Antivirals in Chronic Hepatitis C Treatment: Real-World Data

Kronik Hepatit C Tedavisinde Doğrudan Etkili Antivirallerin Klinik Etkinliği ve Güvenliği: Gerçek Yaşam Verileri

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ABSTRACT

Objectives: Chronic hepatitis C (CHC) disease is an important health problem that affects approximately one hundred and seventy million people worldwide and can cause cirrhosis and liver cancer. In this study, the efficacy and side effects of new generation direct acting antivirals (DAA) agent on the hepatitis C infection profile were evaluated.

Materials and Methods: This retrospective observational study included 210 eligible CHC patients treated with DAAs. They received sofosbuvir ± ledipasvir ± ribavirin, paritaprevir/ritonavir/ombitasvir/dasabuvir ± ribavirin and glecaprevir/pibrentasvir (GLE/PIB). A hepatitis C virus-RNA level of ≤15 IU/mL at 12 or 24 weeks after the end of treatment was considered a sustained virological response (SVR). The side-effect profile and SVR were recorded, and the data were analyzed.

Results: SVR12 was evaluated in 154 patients, and the rate of SVR was found to be 98% (152/154). At the 24th week after treatment, data of 153 patients were available, and SVR was achieved at a rate of 99% (152/153). During treatment, fatigue and itching were common adverse effects. One patient failed to complete treatment during the treatment period due to adverse effects. The patient receiving GLE/PIB developed and progressively worsened allergic rashes. The treatment could be administered only for 3 weeks, and the treatment was terminated on the basis of the lack of tolerability.

Conclusion: In our study, we concluded that the new generation DAA are highly effective with high SVR rates. It was also concluded that they are safe because of their low and tolerable side-effect profile.

Keywords: Chronic hepatitis C, direct-acting antiviral agents, sustained virologic response, adverse events

ÖZ

Amaç: Kronik hepatit C (KHC) hastalığı, tüm dünyada yaklaşık yüz yetmiş milyon insanı etkileyen ve siroz ve karaciğer kanserine neden olabilen önemli bir sağlık sorunudur. Çalışmada, yeni nesil doğrudan etkili antiviral (DEA) ajanların KHC virüsünün enfeksiyon profilinin tedavisinde etkinliği ve yan etkileri değerlendirilmiştir.

Gereç ve Yöntemler: Retrospektif gözlemsel bir çalışma olarak planlanan bu çalışmaya DEA'larla tedavi edilen 210 uygun KHC hastası dahil edildi. Sofosbuvir ± ledipasvir ± ribavirin, paritaprevir/ritonavir/ombitasvir ± dasabuvir ± ribavirin ve glecaprevir/pibrentasvir (GLE/PIB) tedavileri verildi. Tedavinin bitiminden 12 veya 24 hafta sonra ≤15 IU/mL'lik bir hepatit C virüs-RNA seviyesi, kalıcı bir virolojik yanıt (KVY) olarak kabul edildi. Yan etki profili ve kalıcı virolojik yanıtlar kaydedildi ve veriler IBM SPSS 21 programı ile analiz edildi.

Bulgular: Tedavi bitiminden 12 hafta sonra KVY oranı 154 hastada hesaplandı ve %98 olarak saptandı (152/154). Tedavi sonrası 24. haftada 153 hastanın verileri mevcuttu ve KVY %99 (152/153) olarak analiz edildi. Yorgunluk ve kaşıntı tedavi sürecinde yaygın görülen yan etkilerdi. Bir hastanın tedavisini yan etkiler nedeniyle tamamlayamadığı kaydedildi. GLE/PIB alan bu hastada gelişen alerjik döküntülerin giderek artması üzerine hastaya üç hafta boyunca tedavi verilebildi.

Sonuç: Çalışmamızda yeni nesil DEA'ların yüksek KVY oranları ile oldukça etkili olduğu sonucuna varılmıştır. Ayrıca, düşük ve tolere edilebilir yan etki profili gösterdikleri için güvenli olarak değerlendirilmiştir.

Anahtar Kelimeler: Kronik hepatit C, direkt etkili antiviral ajanlar, kalıcı virolojik yanıt, yan etkiler

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Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver diseases worldwide (1). Up to 85% of HCV-infected patients cannot achieve virus clearance and develop chronic infection. Because of chronic infection, liver fibrosis, cirrhosis, extrahepatic involvement, and hepatocellular carcinoma (HCC) may develop in patients (2).

Epidemiological studies in Turkey have shown that chronic hepatitis C (CHC) infection occurs in approximately 1% of the Turkish population, with genotype 1 being the common genotype (92.1%), followed by genotypes 2, 3, and 4 (3). Direct-acting antiviral (DAA) drugs used in the treatment of HCV inhibit the NS3/4A, NS5A, and NS5B regions in the virus genome by stopping the replication of the virus (4).

In our study, we aimed to evaluate the effectiveness and safety of DAA agents available in our country for treating chronic HCV infection in a heterogeneous group of patients.

Materials and Methods

The study was approved by the Ethics Committee for Clinical Research at the Eskişehir Osmangazi University, conforming to the protocols in accordance with the Declaration of Helsinki (approval number: 18/2020).

This retrospective observational study included 172 patients who received DAA treatment with CHC diagnosis in a university hospital infectious diseases and clinical microbiology outpatient clinic between July 2016 and December 2019 and whose persistent virological response level could be assessed after treatment. The distribution of patients is summarized in Figure 1.

The treatment and post-treatment responses of the patients were recorded in the outpatient clinic patient files and the hospital information management system.

Data were collected during treatment and 12 and 24 weeks after treatment. Demographic, clinical, and laboratory parameters (blood count, creatinine, liver panel, prothrombin time/international normalized ratio, viral serology, HCV-RNA level and genotype, liver biopsy findings, radiologic findings, previous treatment) were recorded for all patients. Data on tolerability and safety analyses, adverse events (AE), and drug discontinuation rates owing to AEs were recorded.

Virological response rates were analyzed according to the HCV-RNA levels of the patients. The presence of HCV-RNA was studied by nucleic acid extraction and quantitative real-time polymerase chain reaction (PCR) (artus hepatitis C QS-RGQ, Qiagen). The detection limit of the test used was 15 IU/mL. Genotype determination was performed using real-time PCR using the Bosphore HCV Genotyping Kit V3 and the Montania 4896 device (Anatolia Diagnosis and Biotechnology products, Turkey). In this method, the required HCV-RNA level to detect the HCV genotype is >100 IU/mL. All tests were performed according to the manufacturer's instructions.

Histopathological diagnosis using the liver modified histological activity index (HAI) and ISHAK scoring systems was performed. Those with fibrosis stage F0-3 according to the ISHAK score were non-cirrhotic and those with F4-6 were considered cirrhotics. The decision regarding the agent used in the treatment, its duration, and dose has been made by considering the Communique on Health Practices in our country, both national and international.

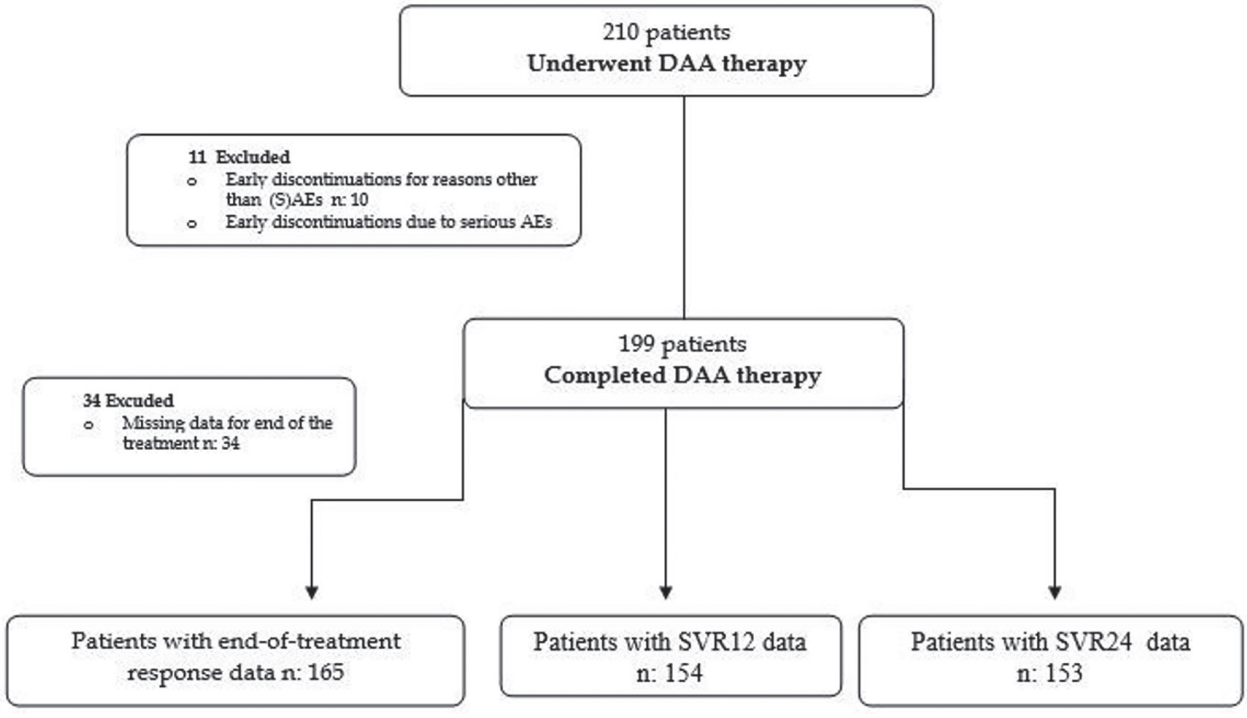

Figure 1. Flowchart showing the distribution of the study populations

DAA: Direct acting antivirals, SVR12: Sustained virological response 12 weeks after treatment, SVR24: Sustained virological response 24 weeks after treatment

Statistical Analysis

Data analysis was performed using IBM Statistical Package for Social Sciences version 21.0. Summary values of quantitative variables are shown as mean ± standard deviation or median (Q1-Q3), summary values of qualitative variables are shown as frequency and percentage. The conformity of quantitative variables to normal distribution was investigated using the Shapiro-Wilk test. Comparison of two independent groups was performed using the Mann-Whitney U test because normal distribution was not found. The relationship between qualitative variables was evaluated using chi-square analysis. The cases obtained with a p-value <0.05 because of the analysis were considered significant.

Results

Patient Characteristics

The clinical and demographic characteristics of the patients are presented in Table 1. The patients included in the study were 49.4% male (n=85) and 50.6% (n=87) female (Table 1). The mean age of all patients was 56.39±15.47 15.47 years (18-81). The mean duration of diagnosis of CHC was 5.4±5.93 (0.5-30) years. Of the patients, 69.8% (n=120) were naive, and 30.2% (n=52) had previously received interferon-based treatment. The most common genotype in the HCV genotype distribution of patients was genotype 1 (1a+1b) in 84.9%, followed by genotypes 3, 2 and 4, respectively. At the beginning of treatment, most patients were non-cirrhotic (84.9% non-cirrhotic, 15.1% cirrhotic). All cirrhotic patients had compensated cirrhosis, and there was no patient with decompensated cirrhosis.

The most common chronic disease in the patients was hypertension at a rate of 40% (n=70), diabetes mellitus 22% (n=38) and asthma 15.6% (n=27) were other common comorbid diseases. There was one human immunodeficiency virus-positive patient with coinfection, and there was no patient with hepatitis B virus infection.

Table 1. Demographic and clinical characteristics of patients

	n (%)
Sex	
Male	85 (49.4)
Female	87 (50.6)
Age	
18-64	112 (65.1)
≥65	60 (34.9)
Genotype	
1a	21 (12.2)
1b	125 (72.7)
2	4 (2.3)
3	20 (11.6)
4	2 (1.2)
Treatment experience	
Naive	120 (69.8)
Experienced	52 (30.2)
Fibrosis stage	
Non-cirrhotic	146 (84.9)
Cirrhotics	26 (15.1)
Total	**172 (100)**

At the beginning of the treatment, the mean alanine transaminase (ALT), aspartate tranaminase (AST), and HCV-RNA levels were 50±43 U/L, 41±24 U/L, and 3139571±5314478 IU/mL, respectively. Liver biopsy results were available in 85.5% (n=147) of the patients before treatment. The mean HAI and fibrosis stage were 6.9±2.1 (3-15) and 2.5±1.3 (0-6), respectively. The mean alpha-fetoprotein (AFP) level studied at the beginning of treatment in the cirrhotic patient group (9.65±16.50 µg/L) was found to be statistically significantly higher than the mean (4.11±3.99) in the non-cirrhotic patient group (p=0.001).

Patients were given 3 separate regimens according to the current treatment options of the study period: the sofosbuvir (SOF)-containing regimen, the paritaprevir/ritonavir/ombitasvir (PRO)-containing regimen, and glecaprevir/pibrentasvir (GLE/PIB) therapy. In some patients receiving SOF- and PRO-based regimens, ribavirin (RBV) treatment was added according to genotype. Of the patients included in our study had different treatment regimen groups; 94 (55.2%) received paritaprevir/ritonavir/ombitasvir ± dasabuvir ± RBV, 62 (36%) received SOF/LDV ± RBV, 15 (8.8%) received GLE/PIB, and 1 received PRO + RBV.

Treatment Efficacy and Sustained Virological Response

In our study, the rate of achieving SVR12 was 98% (152/154), and the rate of achieving SVR24 was 99% (153/154) (Table 2).

The rate of patients achieving SVR12 was analyzed according to gender, genotype, treatment regimen, previous treatment status, level of liver damage, and age (Table 3). In terms of reaching SVR12, no statistically significant difference was found in the other groups except for the genotype (Figure 2, 3).

Statistically significant difference between genotypic groups; groups are not homogeneous, the number of patients with genotype 2 and genotype 3 is less than the number of patients with other genotypes; in addition, it was thought that it may be related to the relapse cases seen in these groups.

Safety

Adverse effects were observed during treatment in 49 (28.5%) of 172 patients included in the study. Some patients had more than one side effect. There was 1 patient whose treatment was terminated because of serious side effects and whose treatment could not be completed. The patient who developed pruritus and rash from the first dose of GLE/PIB treatment, which gradually increased, and whose treatment was interrupted because the

Table 2. Overall treatment outcome

	Virological response n (%)
End of the treatment	162/165 (98%)
SVR12	152/154 (98%)
SVR24	152/153 (99%)

SVR12: Sustained virological response 12 weeks after treatment, SVR24: Sustained virological response 24 weeks after treatment

Table 3. The rate of achieving SVR12 and p-values according to the descriptive characteristics of the patients

	SVR12 (+), (n, %)	SVR (-), (n, %)	p
Sex			
Male	71 (97.3%)	2 (2.7%)	0.223
Female	81 (100%)	0	
Age			
18-64	98 (98%)	2 (2%)	0.542
≥65	54 (100%)	0	
Fibrosis stage			
Non-cirrhotic	130 (99.2%)	1 (0.8%)	0.277
Cirrhotics	22 (95.7%)	1 (4.3%)	
Treatment experience			
Experienced	45 (95.7%)	2 (4.3%)	0.092
Naive	107 (100%)	0	
Genotype			
1a	20 (100%)	0	**0.040**
1b	111 (100%)	0	
2	3 (75%)	1 (25%)	
3	16 (94.1%)	1 (5.9%)	
4	2 (100%)	0	
Therapeutic regimen			
SOF/LDV ± RBV	53 (96.4%)	2 (3.6%)	0.288
PRO ± DSV ± RBV	86 (100%)	0	
GLE/PIB	13 (100%)	0	

SVR: Sustained virological response, SVR12: Sustained virological response 12 weeks after the treatment, SOF/LDV ± RBV: Sofosbuvir/ledipasvir ± ribavirin, PRO ± DSV ± RBV: Paritaprevir/ritonavir/ombitasvir ± dasabuvir ± ribavirin, GLE/PIB: Glecaprevir/pibrentasvir

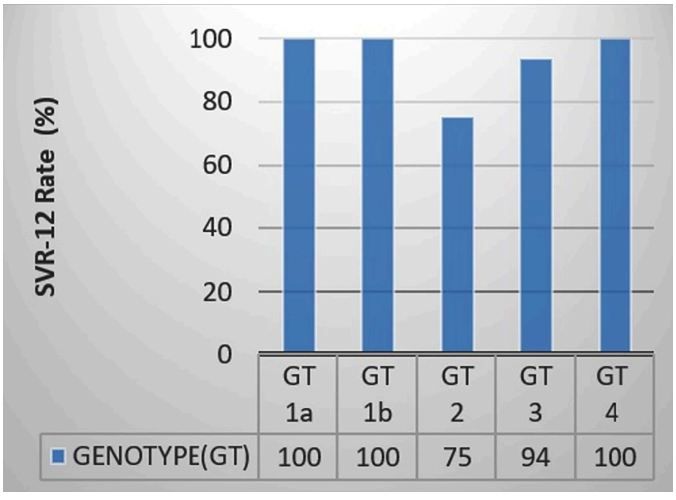

Figure 2. Sustained virologic response 12 rates of different genotypes (p=0.040)

SVR12: Sustained virological response 12 weeks after treatment

condition became intolerable in the 3rd week of treatment was excluded from the study. The most common side effects observed during the treatment process in all patients were itching (11%), weakness (9.3%), and stomach pain (6.4%). Of the 49 patients with side effects, 31 (63.3%) received the PRO-containing regimen, 17 (34.7%) received the SOF-containing regimen, and 1 (2%) received the GLE/PIB-containing regimen. Itching complaints were more common in the PRO regimen, and 15 of 19 patients received the PRO-containing regimen and 4 received the SOF-containing regimen.

Discussion

HCV infection is one of the main causes of chronic liver diseases worldwide. As a result of chronic infection, liver fibrosis, cirrhosis, extrahepatic involvement, and HCC can develop in patients (2). The primary aim of treatment for chronic HCV infection is the prevention of hepatic and extrahepatic complications such as liver necroinflammation, fibrosis, cirrhosis, HCC, and ultimately death by eradicating the HCV. The aim of treatment includes normalization of serum aminotransferases, undetectable HCV-RNA in serum, and improvement of histological findings in the liver.

In many clinical studies evaluating treatment response in patients treated with DAA, mean SVR of over 90% has been demonstrated (5,6). In a multicenter meta-analysis conducted by Perazzo et al. (8), it was found that DAA agents are highly effective. In this study, which included real-life data and more than 57,000 patients, the overall mean of patients with a sustained virological response was 98%. This rate was similar to rates reported in many other observational cohort studies worldwide involving large, real-life data with DAA agents (7-10). In our study, the rate of SVR12 was 98% and that of SVR24 was 99%, similar to other studies in patients who received DAA agents.

In a multicenter study conducted in our country (n=862), they found the rate of SVR12 to be 99.5% in the non-cirrhotic patient group and 95.5% in the cirrhotic patient group. A comparison was made between these two groups according to the cirrhosis status, and they found a statistically significant difference between the groups in terms of response in SVR12 (p<0.016) (11). In our study, the rate of SVR12 was found to be 99% in the non-cirrhotic patient group and 95% in the cirrhotic patient group, and it was found to be lower in cirrhotic patients, similar to other studies.

There are also studies that evaluate the treatment response according to the treatment experience status. In a study conducted by Mizokami et al. (12) in 2021, the rate of SVR12 was determined to be 97.55% in patients with treatment experience and 99.05% in the treatment naive patient group, and it was shown that there was no significant difference between the groups in terms of reaching SVR12. In our study, there was no statistically significant difference in terms of access to SVR between the groups in terms of treatment experience (p=0.092).

In our study, the SVR ratios according to the genotypes of the patients were examined. The response rate was 100% in patients with genotypes 1 and 4, 75% in patients with genotype 2, and 94% in patients with genotype 3. There was a significant difference between genotypic groups in terms of reaching SVR12 (p=0.040).

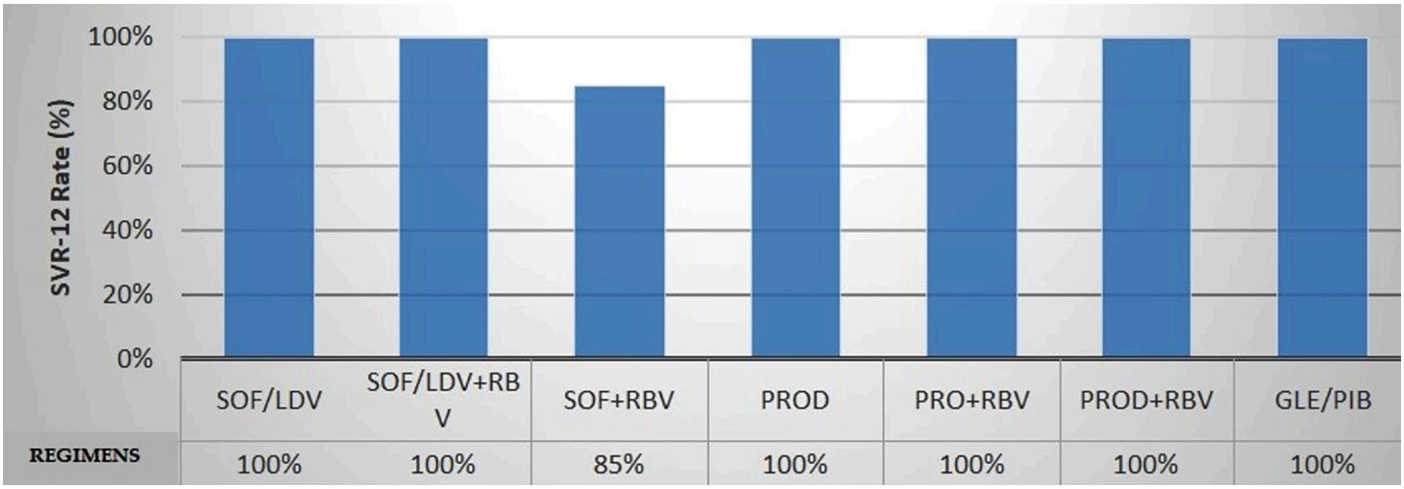

Figure 3. Sustained virologic response 12 rates of each direct-acting antiviral regimen (p=0.288).

SVR12: Sustained virological response 12 weeks after treatment, SOF: Sofosbuvir, LDV: Ledipasvir, RBV: Ribavirin, PROD: Paritaprevir/ritonavir/ombitasvir ± dasabuvir, GLE/PIB: Glecaprevir/pibrentasvir

The reason for the significant difference may be that the distribution of the number of patients among the genotypic groups is not homogeneous. Similar to Turkey, most of the patients in our study were patients with genotype 1 infection. It was thought that this condition developed because of the small number of patients with genotypes 2 and 3 infections and the occurrence of recurrence cases in these groups.

In a retrospective study of 219 patients by Khan et al. (13), it was found that AST and ALT levels were significantly reduced with treatment and reached normal levels in patients who were administered DAAs. In our study, a statistically significant decrease in ALT, AST, and HCV-RNA values during treatment was detected (p<0.001). At the same time, the decrease in gamma-glutamyl transpeptidase and AFP parameters at the end of treatment was statistically significant compared with the start of treatment (p<0.001; p=0.028, respectively). Data on the effect of these biochemical changes on treatment success have not been determined.

In our study, treatments were generally well tolerated and the side effects that developed were mild. The most common side effects were itching (11%), weakness (9.3%), and stomach pain (6.4%). There was one patient whose treatment was interrupted because of intolerance of treatment; the patient who received GLE/PIB treatment did not complete the treatment process because of the increasing rash in the 3rd week of treatment. In the literature, it has been reported that the rate of side effects increases when RBV is added to the treatment. In meta-analyses evaluating SOF/LDV ± RBV treatments, the rate of side effects was higher in groups with RBV; weakness, fatigue, nausea, insomnia, and anemia are reported to be more common (14,15). In our study, 51 patients (29.7%) were receiving RBV-containing DAA treatment, and side effects were similarly more frequent in these patients. Four of the patients already had anemia at the beginning of treatment. However, 17 of the 46 patients (36%) without anemia at the beginning of treatment had anemia at the end of treatment.

In our study, adherence to treatment was quite high in all patients. The SVR rate was as high as 98% in all patients receiving DEA treatment. There was no difference in virological response between the different DAA treatment regimens. There was a significant difference between genotypic groups in terms of SVR. The reason for this difference was thought to be the difference in distribution between the groups and the effect of relapse cases in genotypic groups with a low number of patients. It was found that the cirrhosis status or past treatment experience of the patients did not differ in terms of SVR access.

Study Limitations

Our study was planned retrospectively; therefore, the laboratory and clinical data about the patients were not complete, and the characteristics of the patients and the number of patients in the treatment groups were not evenly distributed as limited aspects of our study.

Conclusion

DEA treatments were evaluated as highly effective and safe because of the low and tolerable side effects.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee for Clinical Research at the Eskişehir Osmangazi University, conforming to the protocols in accordance with the Declaration of Helsinki (approval number: 18/2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.D., E.D.K., Concept: A.D., E.D.K., Design: A.D., E.D.K., Data Collection or Processing: A.D.,

S.N.A., Analysis or Interpretation: A.D., Literature Search: A.D., E.D.K., S.N.A., Writing: A.D.

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Research Article

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Early Viral Kinetics in Patients with Chronic Hepatitis C Treated with Direct-Acting Antivirals

Direkt Etkili Antivirallerle Tedavi Edilen Kronik Hepatit C Tanılı Hastalarda Erken Viral Kinetiğin Tayini

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ABSTRACT

Objectives: We aimed to determine parameters affecting viral kinetics among the first case series of chronic hepatitis C treated with direct-acting oral antiviral drugs in a tertiary university hospital and thus contribute to real-life data on direct-acting antiviral (DAA) treatments.

Materials and Methods: This is a prospective observational study that enrolled patients with chronic hepatitis C infection who were followed up between 2017 and 2019 and administered DAA treatment. Hepatitis C virus (HCV)-RNA (real-time polymerase chain reaction) was detected in the plasma samples of the patients before treatment (day 0) and on the 3rd and 7th days of treatment. Test results below 35 IU/mL were considered negative.

Results: The paritaprevir/ritonavir/ombitasvir/dasabuvir regimen was administered to 21 (44%) patients, sofosbuvir-based regimens to 28 (54%) patients, and glecaprevir-pibrentasvir treatment to 1 (2%) patient. HCV-RNA was detected to be negative significantly earlier in younger patients (p=0.005). The median disease duration was 7 years (range: 2-10), and viral clearance was obtained significantly earlier (p=0.038) in patients with a longer disease duration. The median initial viral load was 3,079,870

ÖZ

Amaç: Üçüncü basamak bir üniversite hastanesinde direkt etkili oral antiviral ilaçlarla tedavi edilen kronik hepatit C'li ilk olgu serilerinde viral kinetikleri etkileyen parametreleri belirleyerek direkt etkili antiviral (DAA) tedavilere ilişkin gerçek yaşam verilerine katkıda bulunmayı amaçladık.

Gereç ve Yöntemler: Bu çalışma prospektif gözlemsel nitelikte olup, 2017-2019 yılları arasında takip edilen, kronik hepatit C tanılı, DAA tedavi başlanması planlanan gönüllü hastalar ardışık şekilde dahil edildi. Tedavinin 0. 3. ve 7. günlerinde plazmada hepatit C virüs (HCV)-RNA çalışıldı. Gerçek zamanlı-polimeraz zincir reaksiyonu platformu olarak COBAS TaqMan HCV test (versiyon 2.0, Roche Molecular Systems, ABD) kullanıldı.

Bulgular: Çalışmaya alınan 50 hastadan 28'i (%56) kadın, yaş ortalaması 58±12,84 idi. Hastalardan 21'ine (%44) paritaprevir-ritonavir-ombitasvir-dasabuvir, 28'ine (%54) ise sofosbuvir içeren ilaçlar, 1'ine (%2) glecaprevir-pibrentasvir tedavisi verildi. Yaşı daha genç olanlarda (p=0,005) ve hastalık süresi daha uzun olanlarda (p=0,038) viral klirensin daha erken sağlandığı saptandı. Başlangıç viral yükü ortancası 3.079.870 IU/mL idi, viral klirensin sağlanma

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(range: 650,925-5,973,029) IU/mL, and no statistically significant correlation was found between the time to negative viral load and initial viral load (p=0.208).

Conclusion: Patients of younger ages and those with a history of longer disease durations became negative earlier, within the first days of treatment. No significant correlation was detected between the initial viral load and early viral kinetics.

Keywords: Viral hepatitis, viral kinetics, hepatitis C, direct-acting antivirals, viral load

süresiyle başlangıç viral yük arasında istatistiksel olarak anlamlı ilişki saptanmadı (p=0,208).

Sonuç: Tedavi sırasında viral yükü erken negatifleşen hastaların daha genç ve hastalık süresi daha uzun olanlar olduğu ortaya çıkmıştır. Başlangıç viral yükle erken viral kinetik arasında ilişki saptanmadı.

Anahtar Kelimeler: Viral hepatitler, viral kinetic, hepatit C, direkt etkili antiviraller, viral yük

Introduction

Chronic hepatitis C continues to be a major public health problem. It is estimated that 58 million people worldwide live with hepatitis C, an average of 1.5 million people are newly infected with chronic hepatitis C annually, and more than 1 million deaths occur each year due to complications of chronic viral hepatitis, including liver cancer and cirrhosis (1).

Hepatitis C virus (HCV) infection (mostly genotype 1) is reported to be responsible for 25% of cases of cirrhosis, 25-30% of hepatocellular carcinoma (HCC), and nearly half of the cases of liver transplantations performed in our country (2).

If left untreated, approximately 80,000 people will develop HCV-related cirrhosis, 3,770 people will develop HCC, and 3,420 people will die from HCV complications in 2030 (2).

Interferon-based regimens were effective in less than half of the cases, despite their long duration of use and serious side effects. Direct-acting oral antiviral drugs, first approved by the FDA in 2011 (3), completely changed hepatitis C treatment, with cure rates over 95%. New drugs were approved over the years, some of which came into use in Turkey after being reimbursed in 2016 (4).

Detection of blood HCV-RNA levels by real-time polymerase chain reaction (PCR), which is the most valid diagnostic tool, is also the most reliable method for monitoring treatment responses.

Although it is well known that direct-acting oral antivirals reduce HCV-RNA levels to an undetectable level in a very short time, there is not enough real-life data on how viral kinetics progress in the early post-treatment period. In this study, we detected HCV-RNA levels before (0^{th} day), on the 3^{rd}, 7^{th} and 90^{th} days of treatment and correlated these results with the alanine aminotransferase (ALT) normalization process (1^{st}, 4^{th}, 12^{th}, and 24^{th} week ALT levels). We aimed to establish real-life data regarding viral kinetic parameters as indicators of sustained viral responses and to contribute to creating up-to-date patient follow-up protocols in the era of direct-acting oral antiviral therapies in Turkey.

Materials and Methods

Patients

Fifty consecutive patients who had been diagnosed with chronic hepatitis C due to HCV-RNA positivity for over six months were planned to undergo direct-acting antiviral (DAA) treatment at the infectious diseases and clinical microbiology outpatient clinic, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine. Informed consent to participate in the prospective observational study was obtained from all patients.

Patients below 18 years of age, pregnant women, those unavailable for consecutive blood test controls, and those who did not give informed consent were excluded.

Methods

Peripheral blood samples obtained from patients via 10 cc EDTA tubes on days 0, 3, and 7 were centrifuged for 10 min at 2000 rpm, and plasma samples were then transferred to 3 separate Eppendorf (1.5 mL) tubes. Samples were stored at -80 degrees celcius until molecular testing. HCV-RNA levels were detected using the RT-PCR method and <35 IU/mL results were accepted as negative (Table 1). The RT-PCR platform COBAS TaqMan HCV Test (version 2.0, Roche Molecular Systems, USA) was used for plasma HCV-RNA detection.

The following data were also retrieved from outpatient case files: HCV-RNA levels detected at first admission or routine monitoring, HCV-RNA levels detected at 3, 6, and 12 months after treatment completion, and routine follow-up data. The parameters to be evaluated in the study were age, gender, comorbidities, infection duration, previous treatment or naivety, viral genotype, treatment modality and duration, biochemical [ALT, aspartate aminotransferase (AST), total bilirubin, alpha-feto-protein], hematological (complete blood count), coagulometric tests (prothrombin time, international normalized ratio), histopathological (liver biopsy), and ultrasound (US) findings.

Treatment success was defined as undetectable HCV-RNA levels (<35 copies/mL) three months after treatment completion and sustainable viral response. Rapid viral response was defined as undetectable HCV-RNA levels at week four. Recurrence was defined as the re-positivity of HCV-RNA within the following period after successful suppression at the end of treatment.

Patients were divided into three groups according to the viral load's negativity detection time.

Group 1: HCV-RNA negatives on 3^{rd} day,

Group 2: HCV-RNA negatives on 7^{th} day,

Group 3: HCV-RNA negatives on 4^{th} week.

The three groups were compared in terms of demographic, virologic (baseline viral load), biochemical, hematological, and histopathological data, duration of disease, receipt of previous inter quartile range-based treatment, and response to DAA drugs according to preferred modalities.

Table 1. Patients' HCV-RNA results during treatment.

Patient no	HCV RNA levels (IU/mL)			
	day 0	3rd day	7th day	Week 4
1.	170160	2 821	51	Negative
2.	667288	175,3	Negative	Negative
3.	115057	Negative	Negative	Negative
4.	497847.6	431.4	0.4	
5.	330 7016	3257.3	581.9	Negative
6.	2533 5572	1106.8	161.9	Negative
7.	1204 573	305.6	2.9	Negative
8.	545816.4	435.1	132.9	Negative
9.	3156376.9	47	Negative	Negative
10.	49 2120	66.2	59.7	Negative
11.	1359400.1	13.6	5.2	Negative
12.	3290 725	1085.6	17.7	Negative
13.	930209.3	163.1	0.1	Negative
14.	427119.8	296.6	2.3	Negative
15.	5540 190	5040.3	123.9	Negative
16.	69 06 16	97.1	11.2	Negative
17.	1152427.7	352.4	Negative	Negative
18.	3753603	145	Negative	Negative
19.	2060133.5	12.	Negative	Negative
20.	45 74 33	Negative	Negative	Negative
21.	14819597.7	4 330	23743.4	Negative
22.	256157.2	272.1	60.7	Negative
23.	5894 639	302:	Negative	Negative
24.	1049279.1	Negative	<35	Negative
25.	1572073.7	225.8	30.	Negative
26.	6208199.9	124.8	Negative	Negative
27.	4165828.3	0.4	28.3	Negative
28.	4741047.7	1600.7	<35	Negative
29.	7895 671	Negative	Negative	Negative
30.	2382.4	816.9	1 624	Negative
31.	8500571.1	1635.9	569	Negative
32.	11131113.1	487.6	2266.6	Negative
33.	1893169.1	211.2	11.3	Negative
34.	3003365	709.6	76	Negative
35.	5008178.8	15653.1	1 335	Negative
36.	12941.7	6203.5	4 599	Negative
37.	10612291.4	2155.3	567.4	Negative
38.	197155	2.3	Negative	Negative
39.	4764603.9	216.4	Negative	Negative
40.	1522195	10.5	Negative	Negative
41.	7 9 831	Negative	Negative	Negative
42.	2812415.5	Negative	Negative	Negative
43.	10497565.7	622.8	47	Negative
44.	5142276	Negative	Negative	Negative
45.	11181199.4	2431.3	266.4	
46.	712609.9	44.7	Negative	Negative
47.	5575319.1	Negative	Negative	Negative
48.	821735.9	7.5	Negative	Negative
49.	7058061.3	2274.6	813	Negative
50.	601835.6	1344.2	Negative	Negative

Statistical Analysis

Statistical analysis was performed using SPSS version 21. Descriptive analyses included data in percentage, frequency, mean ± standard deviation, median, and interquartile range. The distribution of continuous data was assessed using the Kolmogorov-Smirnov test, Shapiro-Wilk test, histogram, and Q-Q graph. For the qualitative variables, McNemar's test was used in the dependent groups, and for the independent groups, the Pearson chi-square test was used. The Pearson chi-square test was used in cases where the conditions cannot be met, and Fisher's exact test was used. For multiple comparison procedures for non-normally dispersed continuous data, the Mann-Whitney U test was used for Kruskal-Wallis and evaluated using the Bonferroni correction. The p-value was accepted as 0.05.

Results

Of the 50 patients included in our study, 28 (56%) were females with an average age of 58±12.84 years (Table 2). Among the

Table 2. Baseline characteristics of patients

Feature	n (%)
Age (mean ± standard deviation, years)	58±12.84
Gender (male/female, n, %)	28 (56%)/22 (44%)
Duration of illness (median, range)	7 years (2-10 years)
Genotype	
1b	39 (78)
1a	5 (10)
2a	2 (4)
3a	4 (8)
Treatment history	
Naive	18 (36)
Pegylated interferon/ribavirin	30 (60)
Sofosbuvir-ledipasvir/ribavirin	1 (2)
Not known	1 (2)
US findings	
Normal findings	27 (56.2)
Chronic liver disease	11 (22.9)
Compensated cirrhosis	8 (16.7)
Decompensated cirrhosis	2 (4.2)
Treatment regimens	
PrOD	14 (28)
PrOD/Ribavirin	7 (14)
SOF/LDP	13 (26)
SOF/LDP/Ribavirin	11 (22)
SOF/DAC	2 (4)
SOF/ribavirin	2 (4)
Glecaprevir-pibrentasvir	1 (2)
Histological Activity Index* (median)	6 (5-7)
Fibrosis score* (median)	3 (1-6)

*According to Modified Ishak's scoring system, PrOD: Paritaprevir/ritonavir/ombitasvir/dasabuvir, SOF: Sofosbuvir, DAC: Daclatasvir

patients, seven (14%) had chronic renal failure (CKF) and six (12%) had diabetes mellitus (DM). Ten (20%) patients were cirrhotic, while 40 (80%) were non-cirrhotic. No significant difference was detected in terms of treatment results between the genders.

By age comparison, younger subjects were found to have negative HCV-RNA levels significantly earlier (p=0.005). Compared among groups, between group 1 and group 3 (p=0.005), and between group 2 and group 3. Among the third group, age was statistically significant (p=0.007). Among the 2nd and 3rd groups, there was a significant age difference (p=0.30) (Table 3).

The median disease duration was 7 years, ranging from 2 and 10 years. For patients with longer disease duration, viral clearance was achieved significantly earlier (p=0.038). A statistically significant difference was detected in disease duration between group 1 and group 2 patients (p=0.014). The median disease duration of patients whose HCV-RNA was negative on the third day of treatment was 10 (6-14) years, and the median disease duration was 2 (1-9) years for those who had negative HCV-RNA on the seventh day, and 4 (3.25-11) years for the patients who were negative on the fourth week.

No significant difference was detected between the patients (n=30) who had a previous history of interferon-based therapy and naive patients (n=20) in terms of treatment outcomes (p=0.973).

In genotype distribution analysis, 39 patients (78%) were identified as genotype 1b. The average fibrosis score (F) of 21 patients who had undergone liver biopsy was determined as 3

Table 3. General characteristics of patients according to their group distribution

	Before treatment (day 0)	**HCV-RNA 3rd day negatives (n=13)**	**HCV RNA 7th day negatives (positive on 3rd day) (n=19)**	**HCV-RNA 4th week negatives (positive on 3rd and 7th days) (n=17)**	**p**
M/F ratio	22 of 28	7.6	6/13	8/9	0.417[a]
Age					
Mean ± SD Median (IQR)	58±12.84 58 (50.75-64.5)	51.31±14.82 52 (43.5-60.5)	56.42±7.66 57 (51-62)	66.06±11.88 64 (58.5-77)	**0.005[b]**
Disease duration[§] (years)	7 (2-10)	10 (6-14)	2 (1-9)	4 (3.25-11)	**0.038[b]**
Previous INF use (%)	30 (60%)	8 (61.5%)	11 (57.9%)	11 (64.7%)	0.973[a]
Genotype 1b ratio (%)	39 (78%)	12 (92.3%)	14 (77.8%)	13 (76.5%)	0.585[c]
Viral load[§] (IU/mL)	3,079,870.5 (650,925-5,973,029.25)	1,359,400 (381,375 -3,489,122)	3,156,376 (712,610-4,764,604)	5,008,179 (400,986.5-1,0554,928.5)	0.208[b]
HAI[§]	6 (5-7)	5.5 (4.5-6.25)	6 (5-8)	6 (5.5-9.5)	0.297[b]
Fibrosis score[§]	3 (1-6)	1 (0.75-3)	3 (2.5-4)	3 (1.75-5)	0,114[b]
ALT[§] (IU/L)	60.5 (33.75-75.5)	55 (27.5-97.5)	57 (29-73)	61 (38-76)	0,830[b]
AST[§] (IU/L)	45.5 (36.5-73.5)	38 (29.75-83.75)	42.5 (36-83)	54 (41-72)	0,399[b]
T. bilirubin[§] (mg/dL)	0.665 (0.53-0.797)	0.56 (0.34-1.035)	0.65 (0.49-1.05)	0.75 (0.63-0.79)	0,250[b]
WBC[§] (10^3/uL)	5 900 (5 100-7200)	6 500 (5 300-7100)	5 900 (5225-8235)	5 400 (4 930-6 335)	0,204[b]
HGB[§] (g/dL)	13.7 (12.47-14.7)	14.1 (12.15-14.75)	13.7 (13.2-14.1)	13.5 (11.05-14.57)	0,547[b]
PLT[§] (10^3/uL)	173,000 (120,500-217,500)	210,000 (155,500-257,000)	173,000 (81,000-220,000)	126,500 (74,250-195,250)	0,09[b]
Treatment regimens					
PrOD (%)	21 (44%)	5 (23.8%) (5/21); (38.5%) (5/13)	8 (38.1%) (8/21); (44.4%) (8/19)	8 (38.1%); (47.1%)	0.893[a]
Sofosbuvir-based treatment (%)	28 (54%)	8 (29.6%); (61.5%)	11 (37%); (55.6%)	9 (33.3%); (52.9%)	0.893[a]
Glecaprevir-pibrentasvir	1 (2%)	0 (0%)	1 (100%); (5.3%)	0 (0%)	-

SD: Standard deviation, IQR: Inter quartile range, INF: Interferon, HAI: Hepatic Activity Index, PROD: Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir, [§]Median values are given (interquartile range), [a]Pearson chi-square test was used, [b]Kruskal-Wallis's test was used, Fisher's exact test was used

(range 1 to 6) and the histological activity index (HAI) was 6 (range 5 to 7) according to the modified Ishak scoring system. In this respect, no statistically significant difference was observed in the HCV-RNA-negative periods (p=0.297).

Abdominal ultrasonography (USG) was normal in 27 patients (56%), chronic liver disease was detected in 11 patients (22.91%), compensated cirrhosis was detected in 8 patients (16.66%), and decompensated cirrhosis was detected in 2 patients (4.16%). Two patients (4.16%) had no USG data.

Patients had mean levels of ALT 60.5 (range: 33.75 to 75.5) IU/mL, AST 45.5 (range: 36.5 to 73.5) IU/mL, and total bilirubin 0.665 (range: 0.53 to 0.797) mg/dL before treatment. Transaminase levels, which were above normal at the beginning, all returned to normal levels at the first week of treatment.

Twenty-one (44%) patients received paritaprevir+ritonavir+ombitasvir/dasabuvir, 28 (54%) patients received sofosbuvir (SOF), and 1 (2%) received glecaprevir-pibrentasvir. Treatment durations were 12 weeks for 44 patients (86%), 24 weeks for 6 patients (12%), and 8 weeks for 1 patient (2%).

Ribavirin was administered in 8 (38.1%) patients on paritaprevir/ritonavir/ombitasvir/dasabuvir (PrOD) and 12 (42.9%) patients receiving SOF. The bilirubin increase was not significant in both groups, with an average increase of 0.39 mg/dL at week 4 in the SOF group and an average increase of 0.065 mg/dL in the first week of treatment in the PrOD regime group, which was similar to baseline normal levels at week 4. Bilirubin changes were not related to the receipt of ribavirin.

A total of 33 adverse effects were recorded in 20 patients (40%), and fatigue was the most common (n=12). Others included itching (n=3), erythema (n=3), hyperbilirubinemia (n=3), dry cough (n=2), headache (n=2), heartburn (n=2), anemia (n=2), nausea (n=1), rash (n=1), hypersomnia (n=1), and weight loss (n=1). Adverse effects were similar in both treatment groups (p=0.458) and were observed more densely in the first weeks of treatment, with 11 patients experiencing multiple adverse effects.

The median initial viral load of the patients was 3,079,870 (650,925-5,973,029) IU/mL, and no statistically significant relationship was found between the negativity times and the initial viral load (p=0.208).

Plasma HCV-RNA levels were measured on days 0, 3, 7, 4, 12, and 24. On the third day of treatment, HCV-RNA was detected in 13 patients (22%). In 37 patients (78%), positive findings were observed. On the 3rd day, HCV-RNA was undetectable in 19 of 37 patients (38%) who were HCV-RNA positive and was recorded as positive in 18 patients (36%).

On the 7th day of treatment, HCV-RNA was negative in 32 patients (64%).

In 48 (96%) patients undergoing treatment, HCV-RNA levels were undetectable at week 4 (1 patient died, 1 patient lost to follow-up and therefore results could not be recorded at week 4, and later) and remained negative at week 12. Of the 44 patients treated for 12 weeks, 43 were found to be HCV-RNA-negative at week 24, whereas 1 patient was found to be positive and accepted as unresponsive.

In 47 (97.9%) patients who completed the treatment, a sustained viral response was obtained, and 1 (2%) patient showed no response.

The patient, who was 56 years old and had not received a response, was diagnosed with chronic hepatitis C (genotype 3a) for 4 years. She had decompensated cirrhosis and previously received interferon/ribavirin treatment. When she first received the treatment (SOF/ledipasvir/ribavirin), she could provide it at her own expense and use it for 12 weeks (treatment duration was not sufficient). The second time, the same treatment was administered for 24 weeks, and a sustained viral response was obtained. In both treatments, on days 3 and 7, the HCV-RNA levels of the patient were detectable. During the follow-up period, the patient developed HCC and was treated with chemoembolization and chemotherapy. The patient died during follow-up.

Eighteen patients had negative HCV-RNA levels at week 4, 8 of which were treated with SOF-based regimens and 10 were treated with PrOD. The mean age was 64 years; the mean duration of the disease was 4 (3.25-11) years, and 13 (72%) patients had previous treatment experience. Genotype 1b was the major genotype (n=13), and the remaining genotypes were 3a (n=3), and 1a (n=2). The mean HAI score was 6 (range: 5.5-9.5) over 18, and the fibrosis score was 3 (1.75-5) over 6. USG results of the patients showed findings of cirrhosis in 8, hepatic steatosis in 2, and chronic liver disease in 2. The accompanying comorbidities were DM (n=3), chronic hepatitis B (n=2), delta hepatitis (n=1), CKF (n=2), hypertension (n=2), hyperthyroidism (1), and chronic heart failure (1). The mean baseline viral load of this group was found to be 5,008,179 IU/mL (range: 400,986.5-1,0554,928.5) IU/mL. When comparing this group with those whose initial viral load was negative, no statistically significant difference was detected (p=0.097).

Discussion

This is one of the first studies in our region to focus on early viral kinetics in response to the treatment of chronic hepatitis C with DAAs. We achieved sustained viral response in 47 of 50 patients (97.9%) who were able to complete the treatment protocol. Our results are similar to those of other studies regarding the outcomes with DAAs (5). We found that patients with early viral load negativity had younger ages and longer mean disease durations.

Patients over 40 years of age reportedly have higher proportions of fibrosis (6). Older age has been associated with delayed viral clearance and suboptimal treatment responses (6). Earlier viral clearance in our relatively younger patients confirms the current data.

Despite the small number of patients, baseline viral load did not significantly affect early viral kinetics in our investigation. Using A. linear discriminant analysis technique. Garbuglia et al. (7) examined the potential relationship between sustained virologic response (SVR) and viral kinetics in 33 individuals with viral hepatitis C genotype 1. In their study, plasma HCV-RNA levels were assessed at days 0, 1, 2, 3, 4, 5, 14, 28 and weeks 8, 12, 24 of treatment as well as at weeks 8, 12, 16, 20, and 24 after completion of the

treatment protocol with telaprevir/peg-interferon/ribavirin. There was no significant difference in early viral kinetics between those who could or could not achieve SVR. Remarkably, there was no correlation between SVR and initial viral load, although this study included treatment options before DAA.

In line with some other studies, all patients receiving DAA had normalized ALT, AST, and total bilirubin levels in our cohort (8,9).

Patients whose viral loads did not become negative on the 3rd and 7th days but did so in the 4th week most frequently had DM as a comorbidity. Diabetes is associated with an accelerated progression of chronic hepatitis C-related liver damage and a delayed response to treatment (10,11).

Patients receiving pegylated interferon and ribavirin were separated into groups based on the HOMA index in a study by Desbois et al. (11). Early viral kinetics were assessed by assessing HCV-RNA levels at 48 h, 2, 4, and 12 weeks. It has been shown that insulin resistance impairs viral dynamics regardless of viral genotype and patient ethnic group (11).

Studies focusing on demonstrating early viral kinetics in patients treated with DAA are scarce. Balagopal et al. (12) investigated the relationship between early viral kinetics and liver histopathology in 6 treatment-naive, non-cirrhotic, HIV co-infected (ART suppressed) chronic hepatitis C patients receiving DDA (PrOD or PrOD/Ribavirin) and found 90% decrease in the numbers of infected hepatocytes within 1 week after treatment initiation, indicating a correlation between viral clearance and histopathological improvement (12).

Gambato et al. (13) we investigated early viral kinetics in DAA-treated patients with compensated cirrhosis. The goal of this study was to personalize treatment and reduce the time required to achieve a cure. Blood samples were collected from 74 patients with compensated cirrhosis who were administered DAA at the 4th hour, 8th hour, 24th hour, 2nd day, 3rd day, 4th day, 2nd week, 3rd week, and 4th week. A viral kinetic study was conducted. In the study, 68 patients (92%) were cured. The time required for HCV clearance was shorter in patients with a lower fibrosis score and lower initial viral load, and modeling studies have shown that determining the optimal duration in cirrhotic patients can reduce treatment costs by 40%.

Perpiñán et al. (14) collected blood samples from 71 HCV patients on DAA at the 4th hour, 8th hour, 1st day, 7th day, 2nd week to 4th week to study early viral kinetics. Cure was achieved in 63 of the patients (89%); seven of the eight patients who could not be cured had resistance-related genetic mutations (resistance-associated substitution) at the time of treatment or recurrence. This study demonstrates the significance of early viral kinetics in predicting DAA resistance.

Dahari et al. (15) investigated early viral kinetics in 58 chronic hepatitis C patients (57% of whom were cirrhotic) receiving various DAA regimens and used mathematical modeling to determine recovery time. In the study, in which a sustained viral response was obtained in 99% of the cases, modeling results revealed that 23 (43%), 16 (30%), 7 (13%), 5 (9%), and 3 (5%) patients were cured at the 6th, 8th, 10th, 12th, and 13th weeks of treatment, and shortening of the treatment duration was considered to be cost-effective.

Bertino et al. (16) used mathematical modeling to investigate the efficacy of short-term treatments in patients infected with genotype 1b who were treated with daclatasvir and asunaprevir. Blood samples were collected from patients just before treatment, at the 4th hour, 8th hour, 48th hour, 72nd hour, 1st week, 4th week, 24th week, and 12 weeks after treatment, and their HCV-RNA levels were measured. Of the 95 patients included in the study, 89 (94%) were cured. According to the modeling study, patients with HCV-RNA levels of 15 IU/mL on days 14 and 28 could achieve cure rates of 100% and 98.5%, respectively, with 6 and 8 weeks of treatment.

In the study conducted by Maasoumy et al. (17) including 298 patients, viral kinetics at weeks 0, 1, 2, 4, 8, 12, 16, 20, and 24 were evaluated with 4 different SOF-based treatment regimens. The likelihood of recurrence in genotype 3 patients was found to be significantly correlated with the high HCV RNA levels detected at the second week of SOF/RBV treatment.

While a shorter duration of disease was found to be a favorable factor for SVR with pegylated interferon + ribarivin treatment (18), we found the contrary with direct acting antivirals; the patient who achieved HCV-RNA negativity on the 3rd day of treatment had a longer duration of disease. The duration of the disease, either shorter or longer, has not been shown to be a predictive factor of response previously (19,20).

Conclusion

In our study, 47 of the 48 patients (97.9%) who successfully completed DAA treatment achieved SVR, with only one (2.08%) returning to positive 12 weeks after treatment and evaluated as relapse. However, he was cured after a 24-week re-treatment.

It was determined that patients with a younger age and longer disease duration had earlier viral clearance. However, no association was observed between the initial viral load and early viral kinetics.

Because the recurrence rate was so low (2.08%), no conclusions could be drawn regarding the relationship between early viral kinetics and recurrence frequency. Larger case series can reveal this relationship more clearly.

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Ethics

Ethics Committee Approval: The study was conducted with the approval of the Clinical Studies Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 231341/date: 16.06.2017).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.G., İ.İ.B., R.Ö., S.Y.K., B.M., N.S., Ö.F.T., Design: D.G., İ.İ.B., R.Ö., B.M., Ö.F.T., Data Collection or Processing: D.G., M.A.K.,

A.Ö., K.M., S.Y.K., B.M., G.A., Analysis or Interpretation: D.G., İ.İ.B., R.Ö., M.A.K., A.Ö., K.M., S.Y.K., R.K., G.A., Ö.F.T., Literature Search: D.G., R.Ö., N.S., Writing: D.G., İ.İ.B., R.Ö.

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Research Article

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Treatment Response to Oral Antivirals in Chronic Hepatitis B Patients: Assessment of Polymorphism in the IL-28B Gene (rs809991)

Kronik Hepatit B Hastalarında Oral Antivirallere Tedavi Yanıtı: *IL-28B* Gen Polimorfizminin (rs809991) Değerlendirilmesi

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ABSTRACT

Objectives: Chronic hepatitis C treatment response is strongly associated with interleukin 28B (IL-28B) single nucleotide gene polymorphism (SNP). In this study, we aimed to investigate the association of the IL-28B rs8099917 SNP with the first-year virological response in chronic hepatitis B (CHB) patients receiving antiviral treatment.

Materials and Methods: We enrolled 100 CHB patients over the age of 18 years who had been on oral antiviral treatment for at least a year. IL-28B rs8099917 SNP was analyzed from the blood samples by polymerase chain reaction. The first-year virological response was investigated retrospectively.

Results: No statistically significant association was found between the IL-28B rs8099917 SNP and first-year virological response (p=1.000). The mean age of patients who did not obtain a first-year virological response was significantly lower than that of those who did (p=0.022), and the median values of alanine aminotransferase (xULN) and hepatitis B virus (HBV)-DNA $\log_{10}$ IU/mL were higher (p<0.001 and p<0.001, respectively). The first-year virologic response rate was significantly lower in hepatitis B e antigen-positive patients than in negative patients (p<0.001). In the multivariate model, it was found that having a high HBV-DNA level was strongly linked to not having a first-year virological

ÖZ

Amaç: Kronik hepatit C tedavisine yanıt, interlökin-28B (IL-28B) tek nükleotid polimorfizmi (SNP) ile güçlü bir şekilde ilişkilendirilmiştir. Bu araştırmada antiviral tedavi alan kronik hepatit B (KHB) hastalarında IL-28B rs8099917 SNP'nin birinci yıl virolojik yanıt ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Araştırmaya, en az bir yıldır oral antiviral tedavi gören 18 yaş üstü 100 KHB hastasını dahil ettik. IL-28B rs8099917 SNP, kan örneklerinden polimeraz zincir reaksiyonu ile analiz edildi. İlk yıldaki virolojik yanıt geriye dönük olarak araştırıldı.

Bulgular: IL-28B rs8099917 SNP ile birinci yıl virolojik yanıt arasında istatistiksel olarak anlamlı bir ilişki bulunamadı (p=1,000). Birinci yılda virolojik yanıt sağlanamayan hastaların ortalama yaşı, sağlanabilenlere göre istatistiksel açıdan anlamlı olarak daha düşük (p=0,022), alanin aminotransferaz (xULN) ve hepatit B virüs (HBV)-DNA $\log_{10}$ IU/mL ortanca değerleri daha yüksekti (sırasıyla; p<0,001 ve p<0,001). Birinci yıldaki virolojik yanıt oranı, hepatit B e antijen pozitif hastalarda negatif hastalara göre istatistiksel açıdan anlamlı derecede düşüktü (p<0,001). Çok değişkenli modelde, yüksek düzeyde HBV-DNA'ya sahip olmanın, ilk yılda virolojik yanıtın olmamasıyla güçlü bir şekilde bağlantılı olduğu bulundu (risk oranı: 1,995, %95 güven aralığı: 1,311-3,036, p=0,001).

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response (risk ratio: 1.995, 95% confidence interval 1.311-3.036, p=0.001).

Conclusion: An association between IL-28B SNP and first-year virological response was not found in patients with CHB. Studies assessing different IL-28B SNPs are warranted to understand the factors affecting treatment response.

Keywords: Chronic hepatitis B, single nucleotide polymorphism, treatment response, interleukin-28B

Sonuç: KHB hastalarında IL-28B SNP ile birinci yıl virolojik yanıtı arasında bir ilişki bulunamamıştır. Tedavi yanıtını etkileyen faktörleri anlamak için farklı IL-28B SNP'lerini değerlendiren çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Kronik hepatit B, tek nükleotid polimorfizmi, tedavi yanıtı, interlökin-28B

Introduction

Chronic hepatitis B (CHB) is one of the main causes of cirrhosis and hepatocellular carcinoma, making it a serious health concern. Interferon-alpha (IFN-α) is an antiviral protein used for treating CHB. IFN-λ induces a signaling pathway similar to IFN-α and thus shows antiviral activity. IFN-λ3, also known as interleukin-28B (IL-28B), exerts an antiviral effect via IFN-stimulated gene (ISG) up-regulation (1). Chronic hepatitis C (CHC) treatment response was strongly associated with IL-28B single nucleotide gene polymorphism (SNP) (2,3,4,5). However, studies with peg-IFN treatment and IL-28B SNP in patients with CHB have had conflicting results (6,7,8,9,10), and there are few studies on the response to oral antiviral treatments. The aim of this study was to evaluate the influence of IL-28B rs8099917 SNP and other factors on the first-year virologic response to oral antiviral treatment in patients with CHB.

Materials and Methods

Study Design, Selection of Cases, and Collection of Data

This research is a retrospective descriptive study. We included 100 CHB patients who had received oral antiviral agents for at least one year, aged 18 years and older, and who came to the Ankara Training and Research Hospital, Infectious Diseases and Clinical Microbiology Department from December 1, 2016, to January 1, 2017, in the study. Patients who were not compliant with treatment, were under 18 years of age, had a malignancy, metabolic or immunological disease, CHC or HIV infection, became pregnant during treatment, or received immunosuppressive therapy, systemic corticosteroids, or chemotherapy were excluded. Demographics, laboratory, and treatment information were retrospectively collected from patient records. The patients underwent liver biopsy before treatment. Biopsy results were analyzed as defined by Ishak et al. (11), and modified histological activity index (HAI) scores and fibrosis stages were recorded. Alanine aminotransferase (ALT) values, hepatitis B serology, and HBV-DNA levels measured during therapy were recorded. Hepatitis B surface antigen, anti-HBs, hepatitis B e antigen (HBeAg), and anti-HBe were examined with the (ELISA) method using the Roche Diagnostics/Cobas 6000 e601 analyzer. The HBV-DNA test was performed using a Qiagen polymerase chain reaction (PCR) kit (Artus Qiagen GmbH, Hilden, Germany).

The upper limit of normal (ULN) for ALT was 40 U/L, as determined by laboratory reference ranges. The ALT (xULN) value was calculated using the formula (ALT/ULN) to evaluate how many times the ALT value was the ULN.

The first-year virological response was defined as having an HBV-DNA level below the detectable limit at the end of the first year in patients with CHB treated with oral antivirals.

IL-28B Gene Polymorphism Analysis

Under the supervision of the investigator, 5 mm of the patients' blood was drawn into EDTA tubes. and stored at -80 °C in the laboratory of Ankara Numune Training and Research Hospital until examination. The extraction of genomic DNA from the blood samples was performed using theGeneMATRIX Quick Blood DNA Purification Kit, as per the manufacturer's recommendations. For PCR analysis, PCR buffer, MgCl2, dNTP mix, forward and reverse primers, Taq DNA polymerase, and DNA template components were prepared. The SNP of rs8099917 near IL-28B was investigated. PCR conditions were applied to the prepared samples. The target region of the *IL-28B* gene was amplified in a Kyratec thermocycler using the primer pair TCCATGTGTTTTATTTGTGC and GGAGAATGCAAATGAGAGA. The obtained PCR products were carried out by electrophoresis at 100 volts for 70 min on a 1.5% agarose gel prepared with 1x TAE buffer. The image was taken under UV light with ethidium bromide dye. After purification, PCR products were sent for DNA sequencing, which was performed unidirectionally in Macrogen with an ABI 3730XL automated sequencer device (Applied Biosystems, Foster City, CA) and BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). BLAST analysis was performed using the obtained sequence analysis results and gene bank data for each sample and its type was determined. SNP genotyping analysis was performed by aligning with the sequence analysis results using the online Multalin program.

Statement of Ethics

Research ethics committee approval was obtained from the Ankara Numune Training and Research Hospital Ethics Committee (approval number: 990/2016, date: 29.06.2016). Informed consent was obtained from the patients.

Statistical Analysis

The study statistics were made using the IBM Statistical Package for the Social Sciences (SPSS) Version 22.0 (Armonk, NY: IBM Corp) program. The conformity of the variables to the normal distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Chi-square, Fisher's exact test, independent samples t-test, and Mann-Whitney U tests were used for statistical evaluation. Whether the possible factors identified in the previous analyses to predict treatment outcome

were independent predictors was examined by logistic regression analysis in multivariate analysis. The Hosmer-Lemeshow test was used for model fit. A p-value 0.05 was considered statistically significant. Power analysis was conducted with a power of 80% and a margin of error of 0.05 using the G*Power 3.1.9.2 program. The analysis revealed that a minimum sample size of 64 participants was required to achieve adequate statistical power. The statistical significance level was set at 0.05.

Results

In this study, we enrolled 100 CHB patients who had been on oral antiviral treatment for at least a year. Because one patient was excluded because genotyping could not be performed, 99 patients were included in the study. The mean age of the patients was 44±11.7 years, and 54 (54.5%) were female. The median initial ALT was 30 U/L (minimum-maximum: 6-282 U/L), ALT (xULN) was 0.75 (minimum-maximum: 0.15-7.05) and HBV-DNA value was 4.36 log10 IU/mL (minimum-maximum: 3-10 log10 IU/mL). HBeAg positivity was detected at the beginning of treatment in 20 (20.2%) patients. 22 (22.2%) of the patients were receiving treatment with lamivudine, 20 (20.2%) with telbivudine, 24 (24.2%) with entecavir, and 33 (33.3%) with tenofovir disoproxil fumarate (TDF).

A liver biopsy could not be performed in the two patients before treatment. For patients who underwent biopsy, the median HAI score was 4 (minimum-maximum: 0-14) and the fibrosis stage was 2 (minimum-maximum: 0-5). Genotyping of rs8099917 near IL-28B revealed that 63 (63.7%) patients had the TT genotype and 36 (36.3%) had the non-TT genotype [34 (34.3%) with GT and 2 (2%) with GG]. There was no difference between the TT and non-TT genotype groups in gender, HBeAg positivity rate, mean age, HAI score, fibrosis stage, ALT (xULN), and HBV-DNA log10 IU/mL levels (p>0.05 for each) (Table 1).

Virological Response

The virological response was observed in 77 (77.7%) patients during the first year. No difference in the first-year virological response rate was found between the IL-28B rs8099917 TT and non-TT genotype groups (p=1.000) (Table 1).

The mean age of patients who did not obtain a first-year virological response was found to be significantly lower than that of those who did (p=0.022). The median values of ALT (xULN) and HBV-DNA $\log_{10}$ IU/mL were significantly higher in patients who did not achieve a first-year virological response than those who did (p<0.001 and p<0.001, respectively). HBeAg-positive patients had a significantly lower first-year virological response rate than HBeAg-negative patients (p<0.001) (Table 1). The multivariate model was performed using the variables of age, ALT (xULN), HBV-DNA $\log_{10}$, HBeAg positivity, and IL-28-B rs8099917 TT genotype. Having a high initial HBV-DNA $\log_{10}$ IU/mL level was statistically significant for lack of first-year virological response (risk ratio: 1.995, 95% CI: 1.311-3.036, p=0.001) (Table 2).

Discussion

There were 63.7% TT genotypes and 36.3% non-TT (34.3% GT, 2% GG) genotypes for IL-28B rs8099917 in our study. As stated in other studies, the dominant genotype was found to be TT (8,12,13).

Table 1. Distribution of patients' IL-28B rs8099917 genotypes and first-year virological responses

		IL28-B rs8099917 genotype		p-value	The first-year virological response		p-value
		TT*, (n=63)	Non-TT*, (n=36)		No†, (n=22)	Yes†, (n=77)	
Gender; (n %)	Female	35 (55.6)	19 (52.8)	0.789**	14 (25.9)	40 (74.1)	0.332**
	Male	28 (44.4)	17 (37.8)		8 (17.8)	37 (82.2)	
Age (years)‡; (mean ± SD)		44.2±11.1	43.6±12.8	0.801††	38.9±12.1	45.4±11.2	0.022††
ALT (×ULN)‡; [median (min.-max.)]		0.83 (0.15-7.05)	0.68 (0.35-7.03)	0.948‡‡	1.8 (0.45-4.48)	0.65 (0.15-7.05)	<0.001‡‡
HBV-DNA ($\log_{10}$ IU/mL)‡; [median (min.-max.)]		4.5 (3.3-9)	4.1 (3.3-9.8)	0.779‡‡	7.5 (4-10)	4 (3-9)	<0.001‡‡
HBeAg; (n, %)*‡	Negative	47 (74.6)	32 (88.9)	0.089**	10 (12.7)	69 (87.3)	<0.001§§
	Positive	16 (25.4)	4 (11.1)		12 (60)	8 (40)	
HAI§; [median (min.-max.)]		4 (0-14)	4 (2-11)	0.620‡‡	5 (0-12)	2 (0-5)	0.153‡‡
FS§; [median (min.-max.)]		2 (0-5)	2 (0-4)	0.814‡‡	4 (1-14)	2 (1-5)	0.772‡‡
Antiviral treatment (n %)	Lamivudine	14 (22.2)	8 (22.2)	0.372**	6 (27.3)	16 (72.7)	0.212**
	Telbivudine	16 (25.4)	4 (11.1)		1 (5)	19 (95)	
	Entecavir	14 (22.2)	10 (27.8)		7 (29.2)	17 (70.8)	
	Tenofovir disoproxil fumarate	19 (30.2)	14 (38.9)		8 (24.2)	25 (75.8)	
IL28-B rs8099917 genotype; (n %)	TT		-		14 (22.2)	49 (77.8)	1.000**
	Non-TT				8 (22.2)	28 (77.8)	

*Column percentage, †Row percentage, ‡At the beginning of treatment, §Since liver biopsy did not performed in two patients, the data of 97 patients were used, **Chi-square test was used, ††Independent samples t-test was used, ‡‡Mann-Whitney U test was used, §§Fisher's exact test was used. ALT: Alanine aminotransferase, ULN: Upper limit of normal (accepted as 40 U/L), HBV: Hepatitis B virus, HBeAg: Hepatitis B e antigen, HAI: Histology activity index, FS: Fibrosis score

Table 2. Risk factors for failure to achieve a first-year virological response

Risk factor	RR (95% CI)	p-value
Age	0.953 (0.902-1.007)	0.085
ALT (xULN)*	0.929 (0.553-1.563)	0.783
HBV-DNA (log_{10} IU/mL)*	1.995 (1.311-3.036)	0.001
HBeAg positivity*	3.324 (0.756-14.614)	0.112
IL-28-B rs8099917 TT genotype	1.175 (0.275-5.024)	0.112

*At the beginning of treatment. ALT: Alanine aminotransferase, ULN: Upper limit of normal (accepted as 40 U/L), HBV: Hepatitis B virus, HBeAg: Hepatitis B e antigen, RR: Risk ratio, CI: Confidence interval

It is known that there is a relationship between the CHC treatment response and IL-28B SNPs. The IL-28B rs8099917 TT genotype was associated with a higher virological response to peg-IFN and ribavirin (5), and the GG genotype was associated with a higher early virological response rate to direct-acting antiviral therapy (14). Patients with the rs8099917 TG and GG genotypes had an increased risk of null virological response in dual CHB and CHC infection (15). IL-28B rs12979860 and rs8099917 SNPs were related to the peg-IFN response in patients with chronic hepatitis D (16). However, few studies have investigated the association of IL-28B SNP with oral antiviral treatment response in patients with CHB. No relationship was observed between the IL-28B rs12979860 SNP and virological response to oral antiviral therapy or peg-IFN therapy in patients with CHB (17). Yu et al. (18) found that CHB patients with the rs8099917 GT genotype were associated with better treatment response to lamivudine, whereas Cakal et al. (19) reported that there was no relationship between rs8099917 genotypes and virological response to entecavir, TDF, and tenofovir alafenamide fumarate treatments. In our study, no relationship was found between the IL-28B rs8099917 genotype groups and first-year virological response to oral antiviral treatment in CHB patients (p=1.000). IFN-λ shows antiviral activity by inducing a signaling pathway similar to IFN-α. It is thought that the IL-28B pathway contributes more to the response to hepatitis C virus infection than to hepatitis B virus infection (20). In addition to activating ISG expression, IFN-λ may also induce other antiviral signaling pathways that may be important in the hepatitis C virus (21). This may help explain why we failed to link the IL-28B SNP to the virological response in patients with CHB.

The virological response rates were lower in HBeAg-positive patients treated with entecavir (22) and telbivudine (23) than in HBeAg-negative patients. However, Lim et al. (24) reported that baseline HBeAg status does not affect the virological response of patients with CHB receiving adefovir treatment. HBeAg-positive patients in our study exhibited a lower virological response rate than HBeAg-negative patients, although multivariate analysis did not statistically confirm this link.

Studies have shown a relationship between age and virological response. It has been reported that the rate of virological response to adefovir treatment is higher in older patients (24). A study by Ono et al. (25) evaluated treatment response in patients receiving entecavir. In univariate analysis, being over 40 years of age was found to be a factor associated with the first-year virological response, but no significant relationship was found when multivariate analysis was performed. Similarly, we found that patients with first-year virological response had a higher mean age than those without (p=0.022), but age was not evaluated as a risk factor in multivariate analysis.

Zeuzem et al. (26) reported that HBeAg-positive patients with HBV-DNA values below 9 log_{10} copies/mL and HBeAg-negative patients whose HBV-DNA values were below 7 log_{10} copies/mL before treatment had a higher virological response rate with telbivudine treatment than those with the above. CHB patients receiving entecavir therapy with HBV-DNA levels above 7.3 log_{10} copies/mL were found to have a lower first-year virological response rate (70.4%) than those with lower HBV-DNA levels (88.7%) (27). Ono et al. (25) reported that an HBV-DNA value below 7.6 log_{10} copies/mL was associated with a first-year virological response to entecavir treatment. Consistent with the literature, we found that the median HBV-DNA log_{10} value of patients who did not obtain a first-year virological response was higher than that of those who did (p<0.001) and this relationship was statistically significant in multivariate analyses.

Patients with ALT above 2xULN were found to have a higher virological response rate to telbivudine in the second year of treatment (26). Tsai et al. (28) found that patients with initial ALT values higher than 2xULN showed a better first-year virological response rate. However, Lim et al. (24) reported no significant relationship between ALT levels and the rate of virological response to adefovir therapy. In contrast to other studies in the literature, we found that patients who did not obtain a first-year virological response had a significantly higher median ALT (xULN) value compared with those who did (p<0.001) but this association could not be demonstrated in the multivariate model.

Study Limitations

The first limitation of this study is that it is retrospective. Therefore, examining the factors affecting response to treatment was not comprehensive. As a limitation of the study, it is stated that treatment groups (such as lamivudine, entecavir, etc.) of CHB patients were not shown homogenous distribution according to the retrospective study design. The other limitation is that we only tested one SNP near IL-28B. Hence, evaluation of other IL-28B SNPs could not be performed.

Conclusion

No association between IL-28B rs8099917 SNP and first-year virological response to oral antiviral therapy in patients with CHB was found in our study. There are very few studies in the literature investigating the link between IL-28B SNP and oral antiviral treatment response in patients with CHB. We believe that studies examining not only different IL-28B SNPs but also other cytokine polymorphisms are warranted. Thanks to these studies, it will be possible to identify markers that will help predict treatment response in patients with CHB.

Ethics

Ethics Committee Approval: Research ethics committee approval was obtained from the Ankara Numune Training and Research Hospital Ethics Committee (approval number: 990/2016, date: 29.06.2016).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.İ., Concept: T.İ., Ç.A.H., C.B., S.K., Design: T.İ., Ç.A.H., C.B., S.K., Data Collection or Processing: T.İ., Ş.A.D., S.K., Analysis or Interpretation: T.İ., C.B., Ş.A.D., Literature Search: T.İ., Ş.A.D., Writing: T.İ., Ç.A.H.

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Research Article

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Comparison of Non-Invasive Methods and Liver Biopsy for Detecting Liver Fibrosis Associated with Chronic Hepatitis B

Kronik Hepatit B'ye Bağlı Fibrozisin Saptanmasında Non-İnvaziv Yöntemlerle Karaciğer Biyopsisinin Karşılaştırılması

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ABSTRACT

Objectives: Serological tests and elastography have recently been used more commonly for the detection of liver fibrosis. The aim of this study was to compare the histopathologically confirmed liver fibrosis stage with serological tests and point shear wave elastography (pSWE) in chronic hepatitis B (CHB) patients.

Materials and Methods: Patients who underwent liver biopsy for CHB in the infectious diseases clinic were included. Demographic characteristics, laboratory results, and pSWE measurements were recorded retrospectively. pSWE measurements were evaluated according to the guidelines of the European Federation of Ultrasound Societies in Medicine and Biology.

Results: Thirty-five patients were included in the study, 23 (65.7%) of whom were male. The mean age was 47.2±12.6. Significant fibrosis was found in 15 patients (42.9%) on histopathological evaluation. The mean pSWE value of patients with mild fibrosis was 1.6±0.5 m/sec and with significant fibrosis was 2.2±0.5 m/sec. Significant fibrosis risk was shown to be associated with mean pSWE values (p=0.002) and the accuracy rate was calculated 62.8% (the area under the curve: 0.807). When the cut-off value of pSWE was taken as 1.77 m/sec to determine significant fibrosis (likelihood ratio: 2.67), the sensitivity was 80% and the specificity was 70% (p=0.002). The correlation between pSWE median values with age (r=0.452, p<0.01), body mass index (r=0.673, p<0.01), grade of steatosis (r=0.534, p<0.01), and stage of fibrosis (r=0.633, p<0.01) was calculated.

ÖZ

Amaç: Son zamanlarda karaciğer fibrozisinin tespitinde serolojik testler ve elastografi daha yaygın olarak kullanılmaktadır. Bu çalışmanın amacı kronik hepatit B (KHB) hastalarında histopatolojik olarak doğrulanan karaciğer fibrozisi evresini serolojik testler ve point shear wave elastografi (pSWE) ile karşılaştırmaktır.

Gereç ve Yöntemler: Enfeksiyon hastalıkları kliniğinde KHB nedeniyle karaciğer biyopsisi yapılan hastalar çalışmaya dahil edildi. Demografik özellikler, laboratuvar sonuçları ve pSWE ölçümleri retrospektif olarak kaydedildi. pSWE ölçümleri, Avrupa Tıp ve Biyolojide Ultrason Dernekleri Federasyonu yönergelerine göre değerlendirildi.

Bulgular: Çalışmaya dahil edilen 35 hastanın 23'ü (%65,7) erkekti. Ortalama yaş 47,2±12,6 idi. Histopatolojik değerlendirmede 15 hastada (%42,9) belirgin fibrozis saptandı. Hafif fibrozisli hastaların ortalama pSWE değeri 1,6±0,5 m/sn, belirgin fibrozisli hastaların ise 2,2±0,5 m/sn idi. Belirgin fibrozis riskinin ortalama pSWE değerleriyle ilişkili olduğu gösterildi (p=0,002) ve doğruluk oranı %62,8 olarak hesaplandı (Eğri altında kalan alan: 0,807). Belirgin fibrozisin belirlenmesi için pSWE'nin eşik değeri 1,77 m/sn alındığında (olasılık oranı: 2,67) testin duyarlılığı %80 ve özgüllüğü %70 olarak bulundu (p=0,002). PSWE medyan değerleri ile yaş (r=0,452, p<0,01), vücut kitle indeksi (r=0,673, p<0,01), hepatosteatoz derecesi (r=0,534, p<0,01) ve histopatolojik fibrozis skorları (r=0,633, p<0,01) arasında orta seviyede pozitif ve anlamlı bir korelasyon olduğu gösterildi.

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Conclusion: pSWE is promising; however, it is thought that the method will develop further if pSWE is used more frequently in clinical practice.
Keywords: Chronic hepatitis B, liver fibrosis, point shear wave elastography

Sonuç: pSWE ümit vericidir; ancak pSWE'nin klinik uygulamada daha sık kullanılması durumunda yöntemin daha da gelişeceği düşünülmektedir.
Anahtar Kelimeler: Kronik hepatit B, karaciğer fibrozisi, point shear wave elastografi

Introduction

Hepatitis B virus (HBV) is a global health problem. Regular follow-up of this disease is important because it causes serious complications such as cirrhosis, hepatocellular cancer (HCC), and death in chronic cases (1).

The stage of liver fibrosis in patients is determined by biopsy, the gold standard method. In recent years, non-invasive methods have been used more frequently due to liver biopsy being invasive in nature, risk of complications, difficulty in repeating, and high cost (2).

Non-invasive methods consist of two categories: serological tests and elastography. Serological tests [Aspartate aminotransferase (AST) platelet ratio index (APRI), Fibrosis-4 (FIB-4), FibroTest/FibroSure (Labcorp, United States) etc.] are used more frequently because of ease of administration. However, there are not enough studies related to serological tests that have accurate sensitivity and specificity that can replace histopathological evaluation directly in the literature (3,4). Therefore, it is generally recommended to use these markers in combination with elastography. Elastography is an alternative to biopsy and gives an idea about liver fibrosis according to the degree of hardness of the tissue (5).

This study was conducted to compare the histopathologically confirmed liver fibrosis stage with serological tests and point shear wave elastography (pSWE) in chronic hepatitis B (CHB).

Materials and Methods

Study Design and Ethical Statement

This study was conducted between 01.09.2021 and 01.09.2022 as a descriptive retrospective study. Ethics committee approval was obtained from the Clinical Research Ethics Committee (approval number: 2022/133, date: 12.10.2022). The study was conducted in accordance with the Declaration of Helsinki.

Clinical Data

The inclusion criteria for the studywere as follows: (I) being followed up due to CHB in the infectious diseases clinic between 01.09.2021 and 01.09.2022, (II) having undergone liver biopsy in the interventional radiology, (III) being between the ages of 18 and 85, and (IV) having hepatitis B surface antigen positivity for more than six months. Patients with a diagnosis of viral hepatitis other than HBV infection and incomplete clinical or laboratory data were excluded from the study.

Data Sources, Measurement, and Variables

All patients' age, body mass index (BMI), gender, laboratory results, and pSWE measurements were retrospectively analyzed from hospital records. The test results of all patients obtained immediately before the biopsy day were recorded. Serological fibrosis scores were calculated using the following formulas (5):

FIB-4 = Age (years) × AST (U/L)/[platelet count (10^9/L) × (U/L)]

APRI = [(AST/upper limit of normal AST range) x100]/platelet count

Forn's index = 7.811-3.131 × log (platelet count) + 0.781 × log [gamma-glutamyl transferase (GGT) (U/L)] + 3.467 × log (age) -0.014 × (total cholesterol)

NAFLD = -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glucose or diabetes mellitus (yes = 1, no = 0) + 0.99 × AST/alanine aminotransferase (ALT) ratio - 0.013 × platelet count (×10^9/L) - 0.66 × albumin (g/dL).

All patient measurements were made by the same radiologist who was unaware of patient information. A Siemens Acuson S3000 ultrasound device and curvilinear probe were used for pSWE.

pSWE measurement was performed at a depth of 2-7 cm of the liver capsule from the intercostal space while the patient was in the supine position and holding breath at the end of expiration. Ten measurements were performed for each patient, and the median value of these measurements was given as the pSWE result. pSWE measurements were performed in accordance with the European Federation of Societies for Ultrasound in Medicine and Biology (6).

Grouping Methods for Participants and Definitions

Patients were divided into two groups according to their Metavir fibrosis scores. Patients with pSWE 1.35 m/sec (F0 and F1) were grouped as having mild fibrosis, and patients with 1.35 m/sec and above (F2 and above) were grouped as significant fibrosis (6).

Histopathological evaluation of biopsies is performed according to the Ishak scoring system in our hospital. The patients were divided into two groups according to Ishak fibrosis scores. Patients with fibrosis scores of 0 and 1 were grouped as having mild fibrosis; patients with a fibrosis score of 2 or more were grouped as having significant fibrosis.

Statistical Analysis

SPSS version 22.0 program was used for statistical evaluation. The Kolmogorov-Smirnov "Test of Normality" was used to analyze the conformity of the data to normal distribution, and those with $p>0.05$ were considered to be normally distributed. Risk prediction to distinguish significant fibrosis from mild fibrosis was evaluated using receiver operating characteristic (ROC) analysis. The cut-off value was determined after calculating the likelihood ratio (LR) in the ROC analysis for pSWE measurement. The p-values for all tests were calculated at the $\alpha<0.05$ significance level.

Results

Thirty-five patients who met the inclusion criteria were enrolled in the study. Twenty-three (65.7%) patients were male and 12 (34.3%) were female. The mean age of the patients was 47.2±12.6.

According to the Ishak fibrosis scoring system, mild and significant fibrosis was detected in 20 (57.1%) and 15 (42.9%) patients, respectively. In addition, five or six fibrosis scores were not detected in any patient.

A comparison of the demographic characteristics, laboratory parameters, and pSWE measurements of the patients according to their Ishak fibrosis scores is shown in Table 1. The risk of significant fibrosis increased significantly with age and BMI (p=0.018 and p=0.032). A statistically significant relationship was not found between Ishak fibrosis scores and laboratory parameters and serological tests.

The mean pSWE value of patients with mild fibrosis was 1.6±0.5 m/sec and with significant fibrosis was 2.2±0.5 m/sec. Significant fibrosis risk was associated with mean pSWE values (p=0.002). According to PSWE measurements, mild and significant fibrosis was detected in 7 (20%) and 28 (80%) patients, respectively.

A cross-table of patients with mild and significant fibrosis according to Ishak fibrosis scores and pSWE measurements was performed (p=0.012). The sensitivity and specificity of the pSWE measurements were calculated as 100% and 35%, respectively. The positive predictive value was 53.5%, whereas the negative predictive value was 100%. The accuracy rate of the test was 62.8%.

To analyze the diagnostic performance of pSWE, ROC curve was used based on the fibrosis score determined by histopathological evaluation (Figure 1).

In the ROC curve analysis, which was performed to predict the risk of significant fibrosis, the area under the curve (AUC) was calculated as 0.807 (95% confidence interval: 0.663-0.951). According to the study, when the cut-off value of pSWE was taken as 1.77 m/sec to determine significant fibrosis (LR: 2.67), the sensitivity of the test was 80% and the specificity was 70% (p=0.002).

According to the ultrasound records of the patients, hepatic steatosis was found in 16 patients (45.7%). Five of the patients (14.3%) had grade 1 steatosis and 11 (31.4%) had grade 2 steatosis. Spearman's test was performed to investigate the correlation between the patients' Ishak fibrosis scores and pSWE median measurements, age, BMI, and grade of hepatic steatosis

Table 1. Comparison of the demographic characteristics, laboratory parameters, serological tests, and pSWE measurements of patients according to Ishak fibrosis scores

	Mild fibrosis, (n=20, 57.1%)	**Significant fibrosis, (n=15, 42.9%)**	**Total (n=35)**	**p-value**
Demographic characteristics				
Age (mean ± SD)	43±12.6	53±10.4	47.2±12.6	0.018*
BMI (mean ± SD)	25.7±4.8	29.5±5.1	27.3±5.2	0.032*
Gender (n, %)				
Female	5 (14.3%)	7 (20%)	12 (34.3%)	0.181
Male	15 (42.8%)	8 (22.9%)	23 (65.7%)	
Laboratory parameters median (min.-max.)				
AST, U/L	27.5 (14-122)	25 (14-175)	27 (14-175)	0.505
ALT, U/L	38.5 (15-203)	29 (13-304)	35 (13-304)	0.484
GGT, U/L	22 (12-146)	22 (12-40)	22 (12-146)	0.125
Total cholesterol, mg/dL	174.5 (97-258)	161 (142-290)	166 (97-290)	0.739
Laboratory parameters (mean ± SD)				
Platelet, x10^3/uL	216.1±70.8	238.6±60.2	225.7±66.5	0.328
Albumin, g/dL	4.3±0.2	4.2±0.3	4.3±0.3	0.294
Serological tests median (min.-max.)				
FIB-4	1.1 (0.4-4.3)	0.9 (0.3-3.1)	0.9 (0.3-4.3)	0.443
APRI	0.3 (0.1-1.7)	0.2 (0.1-3)	0.3 (0.1-3)	0.907
Serological tests (mean ± SD)				
Forn's index	4 ± 1.4	4.8±1.5	4.3±1.5	0.125
NAFLD score	0.1±1.2	0.5±0.8	0.3±1.1	0.208
Radiology results (mean ± SD)				
pSWE measurements, m/s	1.6±0.5	2.2±0.5	1.9±0.6	0.002*

*p<0.05 was considered statistically significant; n: number of patients. BMI: Body mass index, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, FIB-4: Fibrosis-4, APRI: AST platelet ratio index, NAFLD: Nonalcoholic fatty liver disease, SD: Standard deviation, min.: Minimum, max.: Maximum, pSWE: Point shear wave elastography

(Table 2). There was a positive and significant correlation between the variables. The strongest relationship was found between the pSWE median values and BMI (Figure 1).

Discussion

Anyone living with CHB infection should be followed up regularly at 3-6 months intervals because of the risk of developing cirrhosis, liver failure, and HCC (7). To prevent cirrhosis and HCC in patients with CHB, it is critical to identify risk factors that may be associated with fibrosis. In a study by Wu et al. (8), the parameters that predict fibrosis in CHB patients were evaluated. As a result; male gender, ≥18 years of age, high α-fetoprotein level and CHB disease with hepatitis B e antigen negative are found as the associated risk factors (8). In another study, advanced age (≥50 years), being overweight (BMI ≥28 kg/m^2), and high triglyceride and ALT levels were found to be independent risk factors for septal fibrosis (9). In our study, it was also shown that the risk of fibrosis increases significantly with age and BMI, significantly (p=0.018 and p=0.032).

In a review, serological tests such as APRI, FIB-4, and FibroSure can also be used for liver fibrosis scoring in patients who cannot undergo biopsy because they are clinically unsuitable. Nevertheless, it also warns that the accuracy rates of these tests are variable in previous studies (10).

In Kim et al. (11), 575 patients evaluated the performance of the APRI and FIB-4 tests in patients who underwent biopsy. While APRI and FIB-4 test results at the beginning of treatment were similar to those of the Ishak scoring system (p<0.01), they were found to be lower in patients followed 240 weeks after treatment. For this reason, it has been emphasized that APRI and FIB-4 scores are not sufficient in the evaluation of liver fibrosis, especially in the treatment follow-up (11). Therefore, it is generally recommended to use these markers in combination with elastography (5).

A meta-analysis by Jiang et al. (12) compared the diagnostic accuracy of pSWE and transient elastography in predicting liver fibrosis. The rate of failed measurement was found to be more than ten times greater for transient elastography than for pSWE (12). In another study, transient elastography was found to perform better than pSWE in detecting significant and advanced fibrosis (13). Studies have shown that the diagnostic accuracy of imaging methods is better, especially in advanced fibrosis stages. The superiority of transient elastography and pSWE has not yet been clearly demonstrated.

In a prospective multicenter study in patients who underwent biopsy for chronic liver disease conducted by Sande et al. (14), the role of factors such as age, gender, and hepatic steatosis in addition to pSWE measurements in the prediction of liver fibrosis was evaluated using logistic regression analysis, and modeling was performed to detect fibrosis. According to the logistic regression analysis applied to all variables in the model, it has been shown that pSWE and hepatic steatosis are variables that contribute to the predictive power of the model. The AUC was calculated as 0.91 when only pSWE was used in the detection of significant fibrosis, whereas it was calculated as 0.944 when hepatic steatosis and pSWE were used together. It has been shown that the diagnostic accuracy of pSWE significantly increases with the inclusion of hepatic steatosis (14).

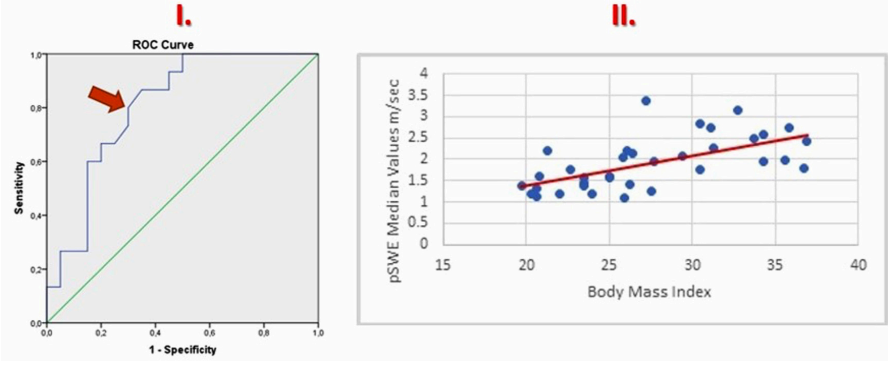

Figure 1. (I) ROC curve for significant fibrosis risk calculated from patients' pSWE measurements (the cut-off value is marked with red arrow.) (II) Correlation graph of BMI and pSWE median values (r=0.673, p<0.01).

ROC: Receiver operating characteristic, pSWE: Point shear wave elastography

Table 2. Correlation between variables

	Age	BMI	Grading of liver steatosis	pSWE median values	Ishak fibrosis scores
Age	1				
BMI	0.561**	1			
Grading of liver steatosis	0.636**	0.591**	1		
pSWE median values	0.452**	0.673**	0.534**	1	
Ishak fibrosis scores	0.520**	0.382*	0.392*	0.633**	1

**p<0.01, *p<0.05 were considered statistically significant. BMI: Body mass index, pSWE: Point shear wave elastography

In Beland et al. (15), 50 patients who underwent liver biopsy were evaluated. When the threshold value for pSWE was taken as 1.89 m/sec in the detection of F2 or higher fibrosis stage in patients followed up with CHC, the sensitivity and specificity were found to be 75% and the AUC was found to be 0.85. A 5% increase in measurements was noted in patients with hepatic steatosis. However, in the multivariate analysis, they could not show a significant correlation between the grade of hepatic steatosis, fibrosis score, and pSWE values (p>0.05) (15). While the cut-off value of pSWE is defined as 1.35 m/sec for detecting F2 or higher fibrosis in guidelines, the cut-off value was calculated as 1.77 m/sec in our study (AUC: 0.807) (6). Therefore, Spearman's correlation test was applied to evaluate the correlation between the variables. There was a moderately positive and significant correlation between pSWE median values and age (r=0.452, p<0.01), BMI (r=0.673 , p<0.01), and grade of hepatic steatosis (r=0.534 , p<0.01). In our study, it was also shown that there was an increase in measurements when patients had hepatic steatosis.

Study Limitations

The limitations of our study are that it was conducted with some patients and was retrospective.

Conclusion

Because liver biopsy has various limitations, non-invasive methods are being investigated more recently. In our study, the diagnostic performance of serological tests and pSWE was evaluated by referring to liver biopsy in patients followed up with CHB. Although serological tests did not give statistically significant results in detecting fibrosis, there was a significant relationship between the significant fibrosis risk and the pSWE median values. pSWE, which can be performed during routine ultrasound imaging with devices of appropriate technology, is promising; however, it is thought that the method will develop further with the new information to be obtained by conducting studies involving more patients.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Clinical Research Ethics Committee (approval number: 2022/133, date: 12.10.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Concept: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Design: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Data Collection or Processing: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Analysis or Interpretation: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Literature Search: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G., Writing: M.F., C.A., M.D., U.B., Y.Ç., R.G., H.C.G.

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Research Article

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Investigation of the Prevalence of HBsAg, Anti-HCV, and Anti-HIV in a Prison in Turkey: A Point Prevalence Study

Türkiye'de Bir Cezaevinde HBsAg, Anti-HCV ve Anti-HIV Prevalansının Araştırılması: Nokta Prevalans Çalışması

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ABSTRACT

Objectives: Access to health services is more difficult for prison inmates than for the general population. This study aimed to determine the prevalence of hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and anti-human immunodeficiency virus (HIV) in prisoners and to determine the rates of risky behavior in terms of these viral diseases using a questionnaire.

Materials and Methods: Nine hundred ninety-three prisoners participated in the Risky Behavior Questionnaire. On March 13-14, 2023, HBsAg, anti-HCV, and anti-HIV were studied by rapid tests in the fingertip blood of 553 volunteer prisoners. Positive samples were re-examined using ELISA.

Results: Out of 1,490 inmates remaining in prison, 993 voluntarily participated in the survey study and 553 participated in the blood control. All participants included in the study were male. The median age was 36 (17-81). Of the participants, 26 (4.7%) HBsAg positivity and 7 (1.3%) anti-HCV positivity were detected. Anti-HCV positivity was found in one (0.2%) of the HBsAg-positive patients and anti-HIV positivity in the other (0.2%), concurrently. Anti-HIV positivity was detected in one patient. The risky behavior questionnaire determined that 522 (54.8%) of the participants had tattoos, 511 (53.6%) had a history of surgery, 384 (10.3%) had unprotected sexual intercourse, 256 (%26,9) had intravenous substance abuse behavior, and 35 (3.7%) had homosexual intercourse.

ÖZ

Amaç: Cezaevlerinde kalan mahkumların sağlık hizmetlerine ulaşmaları genel popülasyona göre daha zor olmaktadır. Bu çalışmada mahkumlar da hepatit B yüzey antijeni (HBsAg), anti-hepatit C virüs (HCV) ve anti-insan bağışıklık yetmezliği virüsü (HIV) prevalansının saptanması ve anket yoluyla bu viral hastalıklar açısından riskli davranış oranlarının belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Riskli Davranış Anketi'ne 993 mahkum katıldı. Toplam 553 gönüllü mahkumdan 13-14 Mart, 2023 tarihinde parmak ucu kanı alınarak hızlı testlerle HBsAg, anti-HCV ve anti-HIV çalışıldı. Pozitif çıkan örnekler ELISA yöntemi ile tekrar edildi.

Bulgular: Cezaevinde kalan mahkum sayısı 1.490 olup, anket çalışmasına 993 mahkum, kan kontrolüne ise 553 mahkum gönüllü olarak katılmıştır. Çalışmaya alınan katılımcıların tamamı erkekti. Ortanca yaş 36 (sınırlar: 17-81) idi. Katılımcılardan 26 (%4,7) kişide HBsAg pozitifliği, 7 (%1,3) kişide anti-HCV pozitifliği saptandı. HBsAg pozitifliği olanların birinde (%0,2) anti-HCV, 1'inde de (%0,2) anti-HIV birlikte pozitifliği tespit edildi. Bir kişide ise anti-HIV pozitifliği saptandı. Riskli davranış anketinde katılımcıların 522'sinin (%54,8) dövme yaptırdığı, 511'inin (%53,6) ameliyat geçirdiği, 384'ünün (%10,3) korunmasız cinsel ilişkide bulunduğu 256'sının (%26,9) damar yoluyla madde kullanıcısı olduğu ve 35'inin (%3,7) eşcinsel ilişkide bulunduğu saptandı.

Sonuç: Çalışmamızdan elde edilen bulgular mahkumlarda güncel hepatit B, hepatit C ve HIV prevalansını göstermektedir.

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Conclusion: The findings of our study show the current prevalence of hepatitis B, hepatitis C, and HIV in prisoners. It is important to detect index cases in prisons and to ensure that they receive treatment, both in the ward and after release, to prevent the spread of diseases in the community.

Keywords: Prisoner, prison, hepatitis B, hepatitis C, anti-HIV

Cezaevlerinde indeks olguların tespit edilmesi, ihtiyacı olanların tedaviye ulaşmalarını sağlamak gerek koğuş içinde gerekse serbest kaldıktan sonra toplumda yayılımı önlemek açısından önemlidir.

Anahtar Kelimeler: Mahkum, cezaevi, hepatit B, hepatit C, anti-HIV

Introduction

The transmission chains of hepatitis B and hepatitis C are similar. The combined infection of these patients with human immunodeficiency virus (HIV) makes the clinic more dramatic as it triggers the development of cirrhosis and cancer, complicating the treatment. Besides the similar transmission routes of all three infections, there is an overlooked transmission route (1-3), which is defined as being over 40 years old and detained for more than 10 years (4,5).

Although clinicians are relieved by the vaccination program for hepatitis B and high treatment success for hepatitis C virus (HCV), measures need to be taken to achieve the goals of reducing HIV infection and deaths associated with these infections (6). The World Health Organization (WHO) recommends taking these precautions because of the mortality-reducing effect and the high cost-effectiveness of treatment (2,6).

Follow-up of hepatitis C, B, and HIV infections in prisoners is important because of the high-risk behaviors in the detainees. 85% of these infections detected in prisons were associated with pre-prison lifetime (7). However, there is a risk of transmission from infected prisoners to other inmates (4). Studies have reported that the prevalence of these infections in prisoners is high (8). Identification and treatment of infected prisoners in a closed environment are also important to prevent the transmission of the disease when they are released into the community. Infected prisoners released back into the community contribute to the spread of these infections. As can be seen, treating patients in closed environments will not only help the detainees but also take a step toward solving an important public health problem by breaking the chain of transmission (3,9). Obtaining epidemiological data on prisoners is one of the primary studies to be conducted in this regard. Prisoners often lack health care before being imprisoned. Infection management can be initiated by detecting infected persons in prisons (6,9,10).

This study aimed to determine the seroprevalence of hepatitis B surface antigen (HBsAg), anti-HCV, and anti-HIV in prisoners and to determine risky behavior rates in terms of these viral diseases.

Materials and Methods

The study was conducted in Samsun t-type Closed Penitentiary Institution between 13 and14 March 2023. The study protocol was approved by the ethics committee of Samsun University Clinical Research Ethics Committee (approval number: 2023/4/4, date: 01.03.2023). Official permissions were obtained from the decision of the T.R. Ministry of Justice General Directorate of Prisons and Detention Houses dated: 20.12.2022 and numbered: 790535500-622.02/E-447/178076, Samsun Chief Public Prosecutor's Office Communication Bureau dated 21.12.2022 and numbered 2022/9860, and Samsun Provincial Health Directorate dated 28.12.2022 and numbered E-26521195-604.02.02.

Risky Behavior Questionnaire and Participants

An 8-question survey was distributed to the convicts who voluntarily participated in the research. The survey included four information questions, including medical information such as age, surgery, blood transfusion, family history of hepatitis B, hepatitis C, and HIV, and four behavioral and attitude questions regarding IV drug use, tattooing, unprotected sexual activity, and homosexual intercouse. No other personal information was requested. The forms filled out anonymously were collected.

Tests

In the second phase of the study, after obtaining signed informed consent forms from 553 volunteer participants, HBsAg (Abbott/Abon, China), anti-HCV (Abbott/Abon, China), and anti-HIV (Abbott/Abon, China) tests were performed in a whole blood sample taken from the fingertip as a screening test. The tests give qualitative results using the immunochromatographic method. In the package inserts, the sensitivity and specificity of the kits are 99.13% and 99.84% for HBsAg, 100% and 100% for anti-HCV, and 100% and 99.96% for anti-HIV, respectively. The working procedure was carried out as specified in the kits; 3 hanging drops of whole blood sample (approximately 75 µLT) taken from the fingertip were dropped into the sample wells of the test device, then 1 drop of buffer was added and the results were evaluated by the microbiologist after 15 min.

Venous blood samples taken from patients with positive HBsAg, anti-HCV, or anti-HIV tests with rapid tests were re-studied by the ELISA method on the Abbott I200 device in the Samsun Training and Research Hospital Medical Microbiology Laboratory.

Statistical Analysis

The data were analyzed using the SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data are given as numbers and percentages.

Results

There were 1,490 detainees and convicts (40 women and the rest men) in the prison. A total of 553 volunteers, 21 women and 532 men, participated in the fingertip screening. HBsAg positivity was observed in 26 (4.7%) participants and isolated anti-HCV positivity in seven (1.3%). Anti-HCV positivity was found in one (0.2%) of the HBsAg-positive patients and anti-HIV positivity in the other (0.2%), concurrently. No isolated anti-HIV positivity was detected. Prisoners with positive rapid screening test results were called for examination in the infectious diseases and clinical

microbiology clinic. All positive samples were confirmed to be positive using the ELISA method.

It was determined in the hospital information management system inquiry that three of the patients with anti-HCV positivity had received previous treatment with a diagnosis of chronic hepatitis C. Two patients were still receiving entecavir treatment with a diagnosis of chronic hepatitis B.

The patient with HIV + HBV co-infection was still receiving antiretroviral therapy. The patient with HBV + HCV co-infection had previously received pegylated interferon (peg-IFN) and ribavirin therapy. Currently, the patient is on hepatitis B treatment. In addition, hepatitis C treatment was started in 1 patient and hepatitis B in 2 patients. Other cases were considered in the inactive phase and followed up.

All 993 volunteers who completed the Risky Behavior Questionnaire were male, with a 66.6% survey participation rate. The median age was 36 (17-81). 522 (54.8%) of the participants had tattoos, 511 (53.6%) had a history of surgery, 384 (10.3%) had unprotected sexual intercourse, 256 (26.9%) had intravenous substance abuse behavior, and 35 (3.7%) had homosexual intercourse (Table 1). The rates were calculated for the people who answered the related questions.

Table 1. Distribution of screening test results for hepatitis B, C, and HIV infection and questionnaire answers for risk factors

	n (%)	Number of participants
Screening tests		
HBsAg	26 (4.3)	553
Anti-HCV	8 (1.3)	
Anti-HIV	1 (0.2)	
HBsAg + anti-HIV	1 (0.2)	
HBsAg + anti-HCV	1 (0.2)	
Risky behaviors		
Tattoo	522 (52.6)	993
Surgery history	511 (53.6)	
Unprotected sex	384 (40.3)	
Intravenous substance abuse	256 (26.9)	
Blood transfusion	235 (24.7)	
Family history	132 (13.9)	
Homosexuality	35 (3.7)	

Risky behavior percentages were calculated from those who answered the related survey questions. HIV: Human immunodeficiency virus, HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus

Discussion

In this study, it was observed that the rates of hepatitis B, hepatitis C, HIV positivity, and some risky behaviors were relatively higher in prisoners than in the general population.

While the general HBsAg positivity is around 4% in our country, it has been reported to be in the range of 4-10 in prisoners (11-13). In a study conducted by Balci et al. (14) in 2008, 2.4% of 633 prisoners were found to be HBsAg positive and 0.5% were anti-HCV positive. The prevalence of hepatitis B in prisoners was higher than the general prevalence in the community. This finding can be attributed to a higher risky behavior history in prisoners compared with the general population. The rate of HBsAg positivity in prisoners was reported 10 times higher than that in the general population in the USA, and 5.6% of the patients were detained during the incubation period (15). Two of the 26 HBsAg-positive patients detected in this study were under treatment. One patient was receiving treatment for HIV and HBV co-infection. Other patients learned about their positivity for the first time. This finding may indicate that there are hepatitis B patients who have not yet been detected in the prisoners, that some of them may be newly infected, that risky behaviors in prisoners may have increased the number of new patients, and that the disease continues to spread in the prison. This also demonstrates the necessity of routine hepatitis B screening in prisons.

According to the 2013 WHO report, the worldwide prevalence of HCV has increased to 2.8%. The report states that this rate is 3.6% (3.2-4.1%) in the North Africa/Middle East region, including Turkey (16). The rate of anti-HCV positivity in the general population in Turkey varies between 0.1% and 0.9% (11,12). In one study, the risk of HCV was 1.9 times higher in those with a prison history than in the normal population (17). HCV positivity in convicts was reported at 20% (2) in Australian prisons, 22.7% in Spanish prisons (18), and 22% in Irish prisons (3). Anti-HCV positivity has been reported as less than 1% in our country and between 0.6% and 3.2% in prisoners (11,12). Balci et al. (14) found anti-HCV positivity in 0.5% of the prisoners in their study. In our study, isolated anti-HCV positivity was found in seven (1.3%) prisoners and hepatitis B and anti-HCV co-positivity in one. This rate is also above the general population prevalence. This finding may be related to the higher risky behavior history in prisoners compared with that in the general population. In the study, it was determined that three of the patients with anti-HCV positivity received previous treatment with a diagnosis of chronic hepatitis C. This finding suggests that the other four patients were previously undetected and/or were newly infected in prison. This indicates that hepatitis C continues to spread in prisons and that routine hepatitis C screening is necessary because of higher risky behaviors in inmates.

Vaux et al. (19) found HIV positivity as high as 59.6% in HCV-positive male homosexual prisoners. A study conducted in Spain also found HIV positivity in 40% of HCV-positive prisoners (18). In another study, the risk of HCV infection was reported to be increased 32.4 times in HIV-positive patients (17). In our study, HBsAg and anti-HCV co-positivity was found in a prisoner, and HBsAg and anti-HIV co-positivity in the other. This finding shows that individuals infected with one of these blood or sexually transmitted viral diseases are most likely to have contracted the second viral infection as a result of continuing their risky behaviors.

In the risky behavior questionnaire, it was determined that a significant proportion of the participants had a history of surgery (53.6%), blood transfusions (24.7%), and family history (13.9%). These risky behaviors are not in the hands of the individual; however, the high prevalence of these stories among prisoners indicates that inmates should be screened for hepatitis B, hepatitis C, and HIV.

Intravenous drug use has been reported to significantly increase the risk of HCV (17,20). In a study conducted in Australia, HCV was found in 19.2% of prisoners using IV drugs, and the relationship between IV drug use and HCV was shown (21). A study conducted in Spain determined that 23.2% of prisoners with HCV are IV drug users and that IV drug use is an independent risk factor for contracting HCV infection, increasing the risk of HCV infection by an average of 55 times. The same study also reported that IV drug use increased the risk of HBV infection by 2.4 times (18). In a study, HCV infection was found in 67% of IV drug users and HBV infection in 50% (22). Although the rate of IV substance use in prisoners varies from country to country, it has been reported as 11% in Canada and 53% in Scotland (23,24). We determined that 26.9% of the prisoners used IV substances. This high rate indicates that these prisoners are also at risk of these viral diseases and should be screened. However, considering that IV substance use is unlikely to continue in prison, it seems that it may be sufficient to screen these prisoners at the end of the possible incubation period at the entrance and after a while.

It has been stated that tattooing in prisoners increases the risk of HCV infection (25). In our study, we determined that 54.8% of the prisoners had tattoos. This rate is well above that of the general population and poses a significant risk of viral diseases. In addition, considering that tattooing continues to be practiced in unhygienic conditions in prison despite the restrictions, it can be suggested that these prisoners should be routinely screened.

It has been reported that risky sexual behaviors in male homosexuals increase the risk of hepatitis B, hepatitis C, and HIV infection (26,27). In a study conducted in France, the rate of HCV positivity in male homosexual prisoners was reported as 1%, and a relationship was found between homosexuality and HCV (19). Todd et al. (28) reported that anal intercourse was an independent risk factor for HBV. Calleja Panero et al. (29) reported that 21% of people infected with HCV showed risky sexual behavior. In our study, we found that 10.3% of the prisoners had unprotected sexual intercourse and 3.7% had homosexual intercourse. Considering the difference between the rates of unprotected and homosexual intercourse revealed in the surveys, it can be thought that a significant part of unprotected intercourse may be related to pre-conviction and/or spousal visitation. Besides, it seems impossible to clearly detect this risky behavior in prison conditions. In the study, 3.7% of the prisoners stated that they had homosexual intercourse. It can be predicted that this rate will be below the real figure due to both the social point of view and the possibility of avoiding expression in prison conditions. It is also unknown whether the same-sex relationship was just pre-conviction or is still ongoing. It does not seem possible to detect the real situation. To prevent the spread of hepatitis B, hepatitis C, and HIV, it may be beneficial for the prison administration to determine the appropriate way and method of educating convicts on these issues.

Study Limitations

There were some limitations in our study. An anonymous questionnaire was used to obtain the data more accurately; therefore, it could not be analyzed which risky behavior might be associated with the viral disease rate because it was not known which participant the answers belonged to. Moreover, although names were not given, it can be considered that most of the rates are below the true rates due to the anxiety that may exist among the detainees. Nevertheless, the number of participants was kept high and it was tried to ensure that the rates caused fewer statistical errors. In addition, the use of tests giving qualitative results in screening can be considered a limitation of our study. However, the ELISA method that gives quantitative results requires a device; that is, it cannot be studied at the bedside. These screening tests are both easier to apply and more cost-effective.

Conclusion

Our study shows the current prevalence of hepatitis B, hepatitis C, and HIV in prisoners and the frequency of risky behaviors. Considering that the risky behavior of the prisoners may continue, routine screening to prevent viral spread and treatment in positive cases will be beneficial both for the health of the person and for preventing transmission.

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Ethics

Ethics Committee Approval: The study protocol was approved by the ethics committee of Samsun University Clinical Research Ethics Committee (approval number: 2023/4/4, date: 01.03.2023).

Informed Consent: It was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.M.Y., M.B., Z.Ş.K., M.A.O., F.T., Concept: E.M.Y., M.B., F.T., Design: E.M.Y., M.A.O., F.T., Data Collection or Processing: E.M.Y., M.B., Z.Ş.K., F.T., Analysis or Interpretation: E.M.Y., F.T., Literature Search: E.M.Y., M.B., Z.Ş.K., M.A.O., Writing: E.M.Y., Z.Ş.K., F.T.

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Research Article

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Health Worker's Knowledge, Attitude, and Practice Toward Hepatitis B Infection at Benghazi Medical Center

Bingazi Tıp Merkezi Sağlık Çalışanlarının Hepatit B Enfeksiyonuna Yönelik Bilgi, Tutum ve Uygulamaları

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ABSTRACT

Objectives: Infection by hepatitis B virus (HBV) among health care workers (HCWs) and its management are one of the pillars of viral hepatitis control and prevention strategies. Health-related behaviors are affected by different aspects of knowledge, attitude, and practice (KAP) toward HBV. The aim of this study was to investigate the relationship between KAP among HCWs and HBV infection at the Benghazi Medical Center.

Materials and Methods: This study used a descriptive case study with a self-administered questionnaire. The data collected between August and November 2021 were coded and analyzed using SPSS software version 23.

Results: The professions correctly answered 67.9% of knowledge questions, 71.0% of attitude questions, and 87.3% of practice questions. A One-Way ANOVA between participants showed significant differences between the profession groups in terms of knowledge scores [14.8; 95% confidence interval (CI): 14.4-15, p=0.001), practice scores (9.2; 95% CI: 8.9-9.5, p=0.00), and attitude scores (3.5; 95% CI: 3.4-3.6, p=0.03). The correlation coefficients between KAP revealed that the attitude and knowledge scores showed a moderately positive relationship that was statistically significant (r=0.403; p=0.001). Among 317 participants, 49% reported they had the vaccine, 33% had not received the vaccine, and 18% were unsure about their vaccine status.

ÖZ

Amaç: Sağlık çalışanları (SÇ) arasında hepatit B virüsü (HBV) enfeksiyonu ve yönetimi, viral hepatit kontrolü ve önleme stratejisinin temel direklerinden biridir. Sağlıkla ilgili davranışlar, HBV'ye yönelik bilgi, tutum ve uygulamanın (KAP) farklı yönlerinden etkilenir. Bu çalışmanın amacı, Bingazi Tıp Merkezi'ndeki SÇ'ler arasındaki KAP ile HBV enfeksiyonu arasındaki ilişkiyi araştırmaktı.

Gereç ve Yöntemler: Bu çalışma, kendi kendine uygulanan bir anket içeren tanımlayıcı bir olgu çalışması kullandı. Ağustos ve Kasım 2021 arasında toplanan veriler, SPSS yazılımı sürüm 23 kullanılarak kodlandı ve analiz edildi.

Bulgular: Meslekler, bilgi sorularının %67,9'unu, tutum sorularının %71'ini ve alıştırma sorularının %87,3'ünü doğru yanıtladı. Katılımcılar arasında tek yönlü bir ANOVA, meslek grupları arasında bilgi puanları [14,8; %95 güven aralığı (GA): 14,4-15, p=0,001), uygulama puanları (9,2; %95 GA: 8,9-9,5) açısından anlamlı farklılıklar olduğunu göstermiştir, p=0.00) ve tutum puanları (3,5; %95 GA: 3,4-3,6, p=0,03). KAP arasındaki korelasyon katsayıları, tutum puanı ile bilgi puanının istatistiksel olarak anlamlı orta düzeyde pozitif bir ilişki gösterdiğini ortaya koydu (r=0,403; p=0,001). Üç yüz on yedi katılımcının %49'u aşı olduğunu bildirdi; %33'ü aşı olmamıştır; ve %18'i aşı durumlarından emin değildi.

Sonuç: SÇ'lerin HBV hakkındaki bilgileri yetersizdir; HBV'nin önlenmesine yönelik olumlu bir tutuma sahiptirler ve HBV'nin önlenmesi için iyi uygulamalara sahiptirler. Araştırmamızdan

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Conclusion: HCWs' knowledge about HBV is inadequate; they have a positive attitude toward the prevention of HBV and have good practices for preventing HBV. Findings from our research emphasized the immediate need to improve HCW training and enable HCW readiness in HB prevention and management.

Keywords: Health care workers, hepatitis B virus, knowledge, attitude and practice

elde edilen bulgular, SÇ'lerin eğitimini iyileştirmeye ve sağlık çalışanlarının HB önleme ve yönetimine hazır olmalarını sağlamaya acil ihtiyaç olduğunu vurguladı.

Anahtar Kelimeler: Sağlık çalışanları, hepatit B virüsü, bilgi, tutum ve uygulama

Introduction

Healthcare workers (HCWs) are susceptible to hepatitis B virus (HBV) infection from infected patients, and HBV-infected HCWs have the potential to infect patients (1). HCWs constitute one of the high-risk groups for this infection because of their repeated exposure, and contact with the body fluids of an infected person is one of the principal modes of transmission of HBV (2). HBV is highly infectious, can be transmitted without visible blood, and remains infectious on environmental surfaces for at least seven days (3). Acute HBV infection can result in chronic hepatitis, which can cause liver cancer, cirrhosis, liver failure, and even death. Guidelines for managing chronic HBV infection in children and adults, including disease monitoring and antiviral therapy, are available (1). In a study conducted by Kermode et al. (4) among 2 million HCWs worldwide, there was a 10-fold higher risk of contracting HBV due to occupational exposure. HCWs in developing countries are at serious risk of infection from blood-borne pathogens, especially in endemic areas such as Sub-Saharan Africa (5). The World Health Organization and the Centers for Disease Control and Prevention (CDC) advise that all HCWs receive an HBV vaccination before beginning their clinical attachments while in medical school as part of occupational safety measures (6). The low level of vaccination and high prevalence of hepatitis B surface antigen found in various studies may be explained by HCWs' lack of knowledge about the transmission route of HBV (7). Several African studies have evaluated the knowledge, attitude, and practice (KAP) of HCWs toward HBV and their vaccination status, showing that KAP by HCWs toward HBV infection is generally inadequate in most developing countries (8). While health-related behaviors are affected by different aspects of KAP, few studies have examined the KAP level of HCWs toward HBV infection in Libya. A study was carried out by Elzouki et al. (9) to determine the prevalence of hepatitis B and hepatitis C among HCWs in five major hospitals in eastern Libya between July 2008 and June 2009. The samples of 601 HCWs were tested to analyze how the risk of HBV and HCV infections is affected by the type of occupation, place of work, working period, and vaccination status. Overall, 52% of HCWs reported receiving full vaccination doses (three doses) against HBV infection. The study explored that HBV vaccines could be provided to HCWs in Libya by scaling up the current vaccination program and implementing the policy of HBV immunization in every healthcare setting as recommended by the CDC.

Materials and Methods

The study was conducted at the Benghazi Medical Center (BMC). A descriptive case study with a self-administered questionnaire was conducted at BMC from August to November 2021. Only the medical and assistant medical staff were included (1029 medical staff and 940 assistant staff).

The sample size was calculated using Epi Information 7 with a 5% margin of error, 95% confidence interval, and 80% study power for the population (1,969). The sample size was 322 (168 medical staff and 154 assistant staff). The questionnaire was adapted from pretested questionnaires used in previous studies. This self-administered questionnaire comprised 44 closed-ended questions divided into four parts. The first part consists of five questions about demographic characteristics and vaccine state (q1-q5); the second part consists of twenty-two questions to assess knowledge regarding HBV infection (q6-q27); the third part consists of thirteen questions investigating the attitude toward HBV infection (q28-q40); and the last part consists of four questions examining the practices of HCWs (q41-q44). A pilot study was conducted on 15 HCWs in BMC to determine the reliability and internal consistency of the KAP questionnaire (10).

The study was approved by the Libyan Authority For Scientific Research (approval number: 2529/22). Permission was obtained from BMC management. Verbal consent was obtained from healthcare workers after the purpose of the study was explained.

Statistical Analysis

The data from the completed questionnaires were coded and analyzed using SPSS version 23. Using a five-point Likert scale, from strongly agree to strongly disagree. Responses that included "agree" and "strongly agree" were coded one if they were the correct answer; otherwise, they were coded 0. Likewise, responses of "disagree" or "strongly disagree" were coded one if it was the correct answer and else coded 0. Correct answers were added to give total KAP scores. A significance test, such as a One-Way ANOVA, was used to examine the difference in mean between the professional groups. The significance level was set at 5% ($p \leq 0.05$). A post-hoc least significant difference (LSD) test was used to examine the least significant difference among the types of professions that were compared between them. The reliability and internal consistency analysis was performed using Cronbach's alpha coefficient, and the validation analysis was performed using the Content Validity Index (11). Pearson's correlation analysis was used to find a relationship between KAP.

Results

Table 1 shows the respondents' sociodemographic characteristics. Of the 322 questionnaires distributed, 317 were completely filled out and collected, for a response rate of (98.4%). Table 2 describes the correct responses to the knowledge questions about the prevention of HBV by HCWs. For the questions "HB can

Table 1. Sociodemographic characteristics of respondents (n=317)

Variables	Frequency	Percentage
Age in years		
18-25	8	2.5
26-33	60	18.9
34-41	101	31.9
42-49	78	24.6
50-57	56	17.7
58-65	14	4.4
Gender		
Female	143	45.1
Male	174	54.9
Profession		
Medical doctor	65	20.5
Nurse	73	23.0
Pharmacist	74	23.3
Lab scientist/tech	59	18.6
Health attendant	46	14.5
Years of practice		
6 months to 10 years	73	23.0
11-20 years	148	46.7
21-30 years	96	30.3
Highest level of education		
Up to secondary school	36	11.4
Diploma	100	31.5
Degree and higher	181	57.1

be prevented by avoiding food not well cooked", and "HB can be prevented by avoiding drinking contaminated water" overall, correct responses to these questions from all HCWs were (41.3%) and (48.3%), respectively, which means poor knowledge. Table 3 provides details of the attitude questions and the positive responses by profession. For question "Do you avoid patients diagnosed with HB?" had 53.8% responded by medical doctors, 42.4% by lab technicians, 33.8 by pharmacists, 32.9% by nurses, and 21.7% by health attendants, which means they had a poor attitude about this point. Although the HBV vaccine is mandated for HCWs, 49% reported that they have received the vaccine, 33% not received and 18% are unsure if they have received the vaccine.

Table 4 provides details of the practice questions and the percentage of respondents with good practice responses by profession. In general, most HCWs had good practices for preventing HBV. Table 5 shows the descriptive statistics for the total KAP score with the type of profession. The overall mean knowledge score for all HCWs was 14.8 (95% CI: 14.4-15.3) which means poor knowledge, while the overall mean attitude score for all HCWs was 9.2 (95% CI: 8.9-9.5) which means a good positive attitude. The overall mean practice score for all HCWs was 3.5 (95% CI: 3.4-3.6) which means good practice.

The result of the P value from a One-Way ANOVA test in terms of KAP scores is described by a post-hoc (LSD) test in Table 6a-c.

In Table 7, the correlation between knowledge score and attitude score was moderately positive, with a statistically significant value of 0.000; this means that as knowledge score rises, so does attitude score, with moderate correlated power. While the correlation between knowledge score and practice score was positive with a statistical significance of 0.000, this means that as

Table 2. Percentage of respondents with correct responses to knowledge questions by profession

Knowledge questions	The type of profession					
	MD, (n=65) (%) correct	N, (n=73) (%) correct	P, (n=74) (%) correct	LT, (n=59) (%) correct	HA, (n=46) (%) correct	Total, (n=317) (%) correct
HBV is 50 to 100 times more infectious than HIV	98.5%	80.8%	87.8%	94.9%	78.3%	88.3%
Hepatitis B can cause liver cancer	100.0%	83.6%	90.5%	94.9%	76.1%	89.6%
Hepatitis B can cause liver cirrhosis	95.4%	87.7%	91.9%	94.9%	69.6%	89.0%
Hepatitis B can be transmitted through the blood and blood products	89.2%	68.5%	79.7%	89.8%	73.9%	80.1%
Hepatitis B can be transmitted through sharp objects and needles	93.8%	72.6%	71.6%	88.1%	65.2%	78.5%
Hepatitis B can be transmitted through sexual intercourse	90.8%	60.3%	64.9%	81.4%	54.3%	70.7%
A healthcare worker can infect patients with hepatitis B infection	73.8%	49.3%	52.7%	61.0%	60.9%	59.0%
Hepatitis B is among the leading causes of death globally	84.6%	71.2%	58.1%	74.6%	63.0%	70.3%
Three doses of HB vaccines are required for full protection	83.1%	67.1%	55.4%	69.5%	60.9%	67.2%
Hepatitis B can be effectively prevented through vaccination	83.1%	68.5%	52.7%	66.1%	58.7%	65.9%
HB can be prevented by proper disposal of sharps and blood	90.8%	67.1%	50.0%	69.5%	54.3%	66.6%

Table 2 Contunied						
HB can be prevented by avoiding multiple sexual partners	87.7%	76.7%	54.1%	74.6%	52.2%	69.7%
HB can be transmitted through drinking contaminated water	93.8%	65.8%	74.3%	79.7%	69.6%	76.7%
HB can be transmitted by handshake or hugging an infected person	87.8%	66.2%	67.6%	62.7%	43.5%	65.6%
HB can be transmitted by faeco-orally	76.9%	32.9%	60.8%	66.1%	39.1%	55.5%
There is no vaccine available for HB infection	73.8%	45.2%	74.3%	72.9%	52.2%	64.0%
A vaccine for HB is available but is not effective	80.0%	39.7%	63.5%	62.7%	37.0%	57.4%
HB can be prevented by avoiding drinking contaminated water	70.8%	31.5%	54.1%	44.1%	39.1%	48.3%
HB can be prevented by avoiding food not well cooked	61.5%	24.7%	47.3%	32.2%	41.3%	41.3%
Hepatitis B virus can cause both acute and chronic infections?	87.7%	60.3%	59.5%	67.8%	56.5%	66.6%
Hepatitis B virus that affects the liver	80.0%	52.1%	58.1%	44.1%	50.0%	57.4%
There is an interval between doses of HB vaccines	87.7%	61.6%	58.1%	55.9%	67.4%	65.9%
Average percentage correct across all questions	85.1%	60.6%	64.9%	70.3%	57.4%	67.9%

MD: Medical doctor, N: Nurse, P: Pharmacist, LT: Lab technicians, HA: Health attendant, HBV: Hepatitis B virus, HIV: Human immunodeficiency virus, HB: Hepatitis B

Table 3. Percentage of respondents with correct responses to attitude questions by profession

Attitude questions	The type of profession					
	MD, (n=65) (%) +ve attitude	N, (n=73) (%) +ve attitude	P, (n=74) (%) +ve attitude	LT, (n=59) (%) +ve attitude	HA, (n=46) (%) +ve attitude	Total, (n=317) (%) +ve attitude
Do you feel at risk by virtue of your work?	87.7%	72.6%	66.2%	71.2%	65.2%	72.9%
Do you feel that you need to be protected from HB infection?	95.4%	74.0%	78.4%	78.0%	67.4%	79.2%
Do you know your HB status?	95.4%	67.1%	87.8%	84.7%	67.4%	81.1%
Do you consider it necessary to receive the HB vaccine?	96.9%	69.9%	85.1%	74.6%	65.2%	79.2%
Will you vaccinate your children against HB?	95.4%	79.5%	78.4%	78.0%	80.4%	82.3%
Will you recommend the HB vaccine to other health HCWs?	87.7%	86.3%	78.4%	74.6%	67.4%	79.8%
Is it important to get the HB vaccine?	98.5%	72.6%	70.3%	81.4%	69.6%	78.5%
Have you completed the HB vaccination schedule?	95.4%	64.4%	68.9%	76.3%	63.0%	73.8%
Does your lifestyle put you at a risk of HB infection?	80.0%	67.1%	63.5%	71.2%	60.9%	68.8%
Is the HB vaccine safe?	83.1%	58.9%	59.5%	67.8%	63.0%	66.2%
Do you takepost exposure prophylactic for HB?	72.3%	49.3%	51.4%	55.9%	60.9%	57.4%
Do you avoid patients diagnosed with HB?	53.8%	32.9%	33.8%	42.4%	21.7%	37.5%
Three doses of vaccine have you received?	76.9%	57.5%	68.9%	59.3%	65.2%	65.6%
Average percentage correct across all attitude questions	86.0%	63.5%	68.5%	70.4%	62.9%	71.0%

MD: Medical doctor, N: Nurse, P: Pharmacist, LT: Lab technicians, HA: Health attendants, HCW: Health care workers, HB: Hepatitis B

knowledge score increases, practice score increases with weakly correlated power. Moreover, the correlation between attitude score and practice score showed a weak positive relationship with a statistical significance of 0.000, which means that when attitude score increases, practice score also increases, with a weakly correlated power.

Discussion

Our study showed a gap in knowledge about HB infection among HCWs; the overall knowledge of HCWs about HB infection was 67.9%. Another study in Khartoum (12) showed that doctors have the highest KAP, which is very close to our study and lower than the 76.9% reported in Nigeria (10). However, the answers to

Table 4. Percentage of respondents with correct responses to practice questions by profession

Practice questions	The type of profession					
	MD, (n=65) (%) good practice	N, (n=73) (%) good practice	P, (n=74) (%) good practice	LT, (n=59) (%) good practice	HA, (n=46) (%) good practice	Total, (n=317) (%) good practice
Do you wear gloves when performing procedures?	92.3%	78.1%	82.4%	81.4%	82.6%	83.3%
Do you wear glasses when performing procedures?	93.8%	79.5%	91.9%	81.4%	82.6%	86.1%
Do you wear a facemask when in direct contact with a patient?	96.9%	84.9%	90.5%	86.4%	87.0%	89.3%
Do you dispose of sharps properly after the procedure?	95.4%	84.9%	90.5%	91.5%	91.3%	90.5%
Average percentage correct across all practice questions	94.6%	81.9%	88.8%	85.2%	85.9%	87.3%

MD: Medical doctor, N: Nurse, P: Pharmacist, LS: Lab technicians, HA: Health attendant

Table 5. Descriptive statistics for knowledge, attitude, and practice (total scores) and professions

	N	Mean	95% CI		Min.	Max.	p
			Lower bound	Upper bound			
Total knowledge score							
Medical doctor	65	18.9	17.8	19.3	11	22	0.001
Nurse	73	13.5	12.3	14.4	5	22	
Pharmacist	74	14.3	13.4	15.1	6	22	
Lab technicians	59	15.5	14.5	16.5	5	22	
Health attendant	46	12.6	11.4	13.9	5	22	
Total	317	14.8	14.4	15.3	5	22	
Total attitude score							
Medical doctor	65	11.2	10.7	11.6	4	13	0.001
Nurse	73	8.5	8.1	8.9	1	13	
Pharmacist	74	8.9	8.4	9.4	5	13	
Lab technicians	59	9.2	8.6	9.6	5	13	
Health attendant	46	8.2	7.6	8.7	5	13	
Total	317	9.2	8.9	9.5	1	13	
Total practice score							
Medical doctor	65	3.8	3.6	3.9	0	4	0.03
Nurse	73	3.2	3.1	3.5	0	4	
Pharmacist	74	3.5	3.4	3.7	0	4	
Lab technicians	59	3.3	3.1	3.7	0	4	
Health attendant	46	3.3	3.1	3.7	0	4	
Total	317	3.5	3.4	3.6	0	4	

CI: Confidence interval, Min.: Minimum, Max.: Maximum

Table 6a. Results of the post hoc LSD test for total knowledge score between the types of profession

(I) profession	(J) profession	p	
Medical doctor	Nurse	0.001	Significant differences
	Pharmacist	0.001	Significant differences
	Lab technicians	0.001	Significant differences
	Health attendant	0.001	Significant differences
Nurse	Medical doctor	0.001	Significant differences
	Pharmacist	0.037	Significant differences
	Lab technicians	0.001	Significant differences
	Health attendant	0.558	No significant differences
Pharmacist	Medical doctor	0.001	Significant differences
	Nurse	0.037	Significant differences
	Lab technicians	0.056	No significant differences
	Health attendant	0.016	Significant differences
Lab scientist/ tech	Medical doctor	0.001	Significant differences
	Nurse	0.001	Significant differences
	Pharmacist	0.056	No significant differences
	Health attendant	0.001	Significant differences
Health attendant	Medical doctor	0.001	Significant differences
	Nurse	0.558	No significant differences
	Pharmacist	0.016	Significant differences
	Lab technicians	0.001	Significant differences

LSD: Least significant difference

some questions revealed a lack of knowledge, such as the fact that 44.5% of participants were unaware that HBV could not be transmitted feco-orally and 23.3% did not know that the virus is not transmitted through drinking contaminated water. In addition, 51.7% were unaware that the virus could not be prevented by avoiding drinking contaminated water, and 58.7% wrongly thought that HBV could be prevented by avoiding food that is not well cooked, which is less than the 63.2% reported by another study in

Table 6b. Results of the post hoc LSD test for the total attitude score between types of professions

(I) profession	(J) profession	p	
Medical doctor	Nurse	0.001	Significant differences
	Pharmacist	0.001	Significant differences
	Lab technicians	0.001	Significant differences
	Health attendant	0.001	Significant differences
Nurse	Medical doctor	0.001	Significant differences
	Pharmacist	0.236	No significant differences
	Lab technicians	0.067	No significant differences
	Health attendant	0.350	No significant differences
Pharmacist	Medical doctor	0.001	Significant differences
	Nurse	0.236	No significant differences
	Lab technicians	0.472	No significant differences
	Health attendant	0.046	Significant differences
Lab technicians	Medical doctor	0.001	Significant differences
	Nurse	0.067	No significant differences
	Pharmacist	0.472	No significant differences
	Health attendant	0.012	Significant differences
Health attendant	Medical doctor	0.001	Significant differences
	Nurse	0.350	No significant differences
	Pharmacist	0.048	Significant differences
	Lab technicians	0.012	Significant differences

LSD: Least significant difference

Table 6c. Results of the post hoc LSD test for the total practice score by profession

(I) profession	(J) profession	p	
Medical doctor	Nurse	0.001	Significant differences
	Pharmacist	0.138	No significant differences
	Lab technicians	0.022	Significant differences
	Health attendant	0.047	Significant differences
Nurse	Medical doctor	0.001	Significant differences
	Pharmacist	0.063	No significant differences
	Lab technicians	0.406	No significant differences
	Health attendant	0.349	No significant differences
Pharmacist	Medical doctor	0.138	No significant differences
	Nurse	0.063	No significant differences
	Lab technicians	0.355	No significant differences
	Health attendant	0.486	No significant differences
Lab technicians	Medical doctor	0.022	Significant differences
	Nurse	0.406	No significant differences
	Pharmacist	0.355	No significant differences
	Health attendant	0.876	No significant differences
Health attendant	Medical doctor	0.047	Significant differences
	Nurse	0.349	No significant differences
	Pharmacist	0.486	No significant differences
	Lab technicians	0.876	No significant differences

LSD: Least significant difference

Nigeria (10). On the other hand, 70.3% of the percentage is large compared to that reported by Samuel et al. (13), who showed that only 14.2% and 9.3% incorrectly identified the feco-oral route and drinking contaminated water as means of transmitting the virus, while 6.2% and 3.1% incorrectly thought that HBV can be prevented by avoiding contaminated water and food that is not well cooked. In our study, 80% of participants said that HBV can cause liver cancer and cirrhosis, which was inconsistent with other studies in Kabul, Afghanistan (8), where 88.24% of participants said it can. This study found that 73.8% of participants completed the HB vaccination schedule, which was lower than the 100% completion rate reported by Kumah et al. (14). Knowledge regarding preventive measures plays a role in the control of HBV. Overall, these results suggest that more knowledge is necessary when providing health education to HCWs, which is typically the first step toward risk reduction and an improvement in the quality of life. In our study, 33.8% of respondents were unsure about the safety of the HBV vaccine, which is lower than the study in Northern Vietnam (15), but higher than the 92.1% reported in Saudi Arabia for HBV vaccine safety. 27.1% of participants did not know

Table 7. Correlation coefficients between knowledge attitude and practice (n=317)

		Total knowledge score	Total attitude score	Total practice score
Total knowledge score	Pearson correlation	1	0.403*	0.236*
	p	-	0.001	0.001
Total attitude score	Pearson correlation	0.403*	1	0.241*
	p	0.001	-	0.001
Total practice score	Pearson correlation	0.236*	0.241*	1
	p	0.001	0.001	-

*Correlation is significant at the 0.01 level (2-tailed)

the risk of contracting HBV by virtue of their work, unlike studies done in Saudi Arabia. 20.2% and 20.8% of respondents felt they did not need to be protected from hepatitis B infection (12). These HCWs were less likely to take HB infection control and prevention measures seriously because they thought they were not at risk of HB infection. 18.9% of participants were unaware of their HBV status, 20.8% had received the hepatitis vaccine, and 73.80% of HCWs were vaccinated, compared with 50.4% of respondents who did not know their HB status (14). Regarding practice toward HB preventive measures, 16.7% of respondents did not wear gloves when conducting procedures; this percentage was less than that in a study conducted in Kabul (62.55%) (8). Another study conducted in Sudan reported a much higher percentage of 92.8% (14). In our study, 90.5% of respondents said they properly disposed of sharps after use. However, overall correct responses to practice from all HCWs were 87.3% "good practice", may be due to the data collected during the coronavirus disease-2019 (COVID-19) period, where HCWs underwent extensive infection control training. Regarding HBV vaccine status among HCWs, this study found that 49% of respondents among 317 participants had received an HBV vaccine, which is very similar to Japan's rate of 48.20% (16). 18% of respondents are unsure if they have received the HBV vaccine, and 33% report that they have not received it. A study by Daw et al. (17) aimed to determine the prevalence of HBV markers among HCWs, investigate some risk factors for such prevalence, and outline specific policies to address these issues among HCWs. The study concludes that HBV vaccine, education, clinical advice, and health insurance should be available for HCWs who are at a higher risk of HBV infection (17).

Study Limitations

To prevent respondents from discussing their answers with others, the questionnaires were completed in the presence of the researcher. Only medical staff and medical assistant staff were involved in the study; other BMC staff such as security staff and administrative office staff were not involved.

Conclusion

This study found that the knowledge of HCWs at BMC about HBV is inadequate. The majority of the staff had poor knowledge responses, a positive attitude, and good practices for preventing HBV. The rate of vaccination indicates the risk, and the main reasons that led to its occurrence were that HCWs were not vaccinated because of a lack of knowledge about vaccination. HCWs who were not vaccinated needed to implement an HBV vaccination program.

Ethics

Ethics Committee Approval: The study was approved by the Libyan Authority For Scientific Research (approval number: 2529/22).

Informed Consent: Verbal consent was obtained from healthcare workers after the purpose of the study was explained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.E., Design: A.E., R.G.O., Data Collection or Processing: R.G.O., Analysis or Interpretation: A.E., R.G.O., Literature Search: A.E., A.B.E., R.G.O., Writing: A.E., A.B.E., R.G.O.

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