Serum HBV RNA as a predictor of virological response in treatment-naive chronic HBeAg-positive HBV-infected patients with normal alanine aminotransferase : Chinese Medical Journal

Current Issue

- Previous Article
- Next Article

Clinical Observation

Serum HBV RNA as a predictor of virological response in treatment-naive chronic HBeAg-positive HBV-infected patients with normal alanine aminotransferase

Qian, Jiandan[1]; Zhang, Chi[1]; Liu, Huaie[1,2]; Wang, Guiqiang[1,3,4]; Zhao, Hong[1,3]

Editor(s): Ji, Yuanyuan

Author Information

[1]Department of Infectious Diseases and the Center for Liver Diseases, Peking University First Hospital, Beijing 100034, China

[2]Department of Infectious Disease, Kunming Medical University First Affiliated Hospital, Kunming, Yunnan 650032, China

[3]Department of Infectious Diseases, Peking University International Hospital, Beijing 102206, China

[4]The Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Zhejiang University, Hangzhou, Zhejiang 310003, China.

Correspondence to: Prof. Hong Zhao, Department of Infectious Diseases and the Center for Liver Diseases, Peking University First Hospital, Beijing 100034, ChinaE-Mail: zhaohong_pufh@bjmu.edu.cn

How to cite this article: Qian J, Zhang C, Liu H, Wang G, Zhao H. Serum HBV RNA as a predictor of virological response in treatment-naive chronic HBeAg-positive HBV-infected patients with normal alanine aminotransferase. Chin Med J 2022;135:2351–2353. doi: 10.1097/CM9.0000000000002122

Received 30 July, 2021

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Website (www.cmj.org).

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. http://creativecommons.org/licenses/by-nc-nd/4.0

Chinese Medical Journal 135(19):p 2351-2353, October 05, 2022. | DOI: 10.1097/CM9.0000000000002122

- Open
- SDC

Metrics

According to current guidelines, patients with chronic hepatitis B virus (HBV) infection whose HBV DNA is positive but whose alanine aminotransferase (ALT) levels are normal do not currently need antiviral treatment.[1] However, studies have found that even chronic HBV infection patients with normal ALT may progress to cirrhosis or hepatocellular carcinoma (HCC). Furthermore, almost half of patients with normal ALT levels were found to have moderate to severe inflammation and/or significant fibrosis.[2] Currently there were only a few studies on the treatment of chronic HBV patients with normal ALT levels, and the factors that affect their virological response (VR) are still unclear. An increasing number of studies have proven that serum HBV RNA can be used as a non-invasive indicator to predict a VR.[3] In this study, we explored the predictive value of HBV RNA in anticipating a VR in normal ALT chronic HBV patients.

A total of 63 treatment-naive adult chronic HBV patients with normal ALT who had undergone liver biopsy and received entecavir therapy were recruited from multicenters. Patients with other types of viral hepatitis coinfection, and other chronic liver diseases, such as genetic or autoimmune liver disease, alcoholic liver disease, non-alcoholic fatty liver disease, and HCC, were excluded. All 63 patients were followed up to 78 weeks with a second liver biopsy. Serum HBV RNA titers were detected by the RNA simultaneous amplification testing method (HBV-SAT) based on real-time fluorescence detection of RNA transcription-mediated nucleic acid amplification using a HBV-SAT kit (Rendu Biotechnology, Shanghai, China) for all 63 patients both at baseline and after 78 weeks of treatment. The complete protocol for this clinical trial has been registered at clinicaltrials.gov (NCT01679769).

Hepatic inflammation was graded using the histology activity index (HAI), and fibrosis was staged using the Ishak fibrosis score (F). HAI <5and F <3 were considered as mild or minimal hepatic inflammation and fibrosis.[2] All statistical analyses were performed using SPSS 21.0 software (SPSS, Inc., Chicago, IL, USA). The figure was created with GraphPad Prism version 6.0 (GraphPad, San Diego, CA, USA).

At baseline, among the 63 patients, the male/female ratio was 1.4:1, and the median age was 41 years. Fifty-three (84%) patients were older than 30 years. Thirty (48%) patients were hepatitis B e antigen (HBeAg)-positive and another 33 (52%) patients were HBeAg-negative. The median serum HBV RNA level (range) was 4.28 (1.70–7.87) $\log_{10}$ copies/mL before treatment. The median HAI and F scores were 5.0 (1.0–11.0) and 3.0 (0–6.0), respectively [Table 1].

Table 1 - Baseline characteristics of treatment-naive chronic HBV patients with normal ALT.

Characteristics	HBeAg-positive (*n* =30)	HBeAg-negative (*n* =33)	Total (*n* =63)	*P* value

Characteristics	HBeAg-positive (*n* =30)	HBeAg-negative (*n* =33)	Total (*n* =63)	*P* value
Male/female	22/8	15/18	37/26	0.026
Age, years	39.5 (22–57)	46.0 (22–62)	41.0 (22–62)	0.469
Age >30 years old, *n* (%)	24 (80)	29 (88)	53 (84)	0.397
BMI, kg/m^2	23.33 (18.42–30.12)	23.43 (14.82–31.14)	23.43 (14.82–31.14)	0.912
PLT, ×10^9/L	152.0 (65–296)	162.0 (62–268)	155.5 (62–296)	0.860
ALT/ULN	0.85 (0.26–0.98)	0.64 (0.28–0.95)	0.76 (0.26–0.98)	0.014
AST/ULN	0.82 (0.44–2.97)	0.72 (0.43–1.46)	0.75 (0.43–2.97)	0.063
TBIL, μmol/L	13.6 (7.18–49.80)	13.2 (4.31–58.5)	13.5 (4.31–58.5)	0.831
AFP, ng/mL	4.37 (1.00–77.37)	2.79 (0.60–113.50)	3.26 (0.60–113.50)	0.172
HBV RNA, $\log_{10}$ copies/mL	5.46 (3.00–7.87)	3.63 (1.70–6.14)	4.28 (1.70–7.87)	<0.0001
HBV RNA undetectable, *n* (%)	0	4 (12)	4 (6)	0.051
HBV DNA, $\log_{10}$ IU/mL	6.34 (3.98–8.66)	4.18 (1.30–7.53)	5.70 (1.30–8.66)	<0.0001
$\log_{10}$ (HBV DNA/HBV RNA)	1.43 (−3.44–3.90)	1.26 (−2.10–3.44)	1.39 (−3.44–3.90)	0.731
qHBsAg, $\log_{10}$ IU/mL	3.57 (1.20–4.92)	3.40 (2.08–4.27)	3.48 (1.20–4.92)	0.106
qAnti-HBc, $\log_{10}$ IU/mL	3.39 (2.42–4.44)	3.88 (2.86–5.00)	3.64 (2.42–5.00)	<0.0001
APRI	0.51 (0.22–1.98)	0.47 (0.16–1.65)	0.48 (0.16–1.98)	0.297
FIB-4	1.63 (0.29–5.93)	1.38 (0.34–4.54)	1.45 (0.29–5.93)	0.683
Fibroscan, kPa	10.7 (4.8–47.2)	8.5 (4.6–20.9)	9.9 (4.6–47.2)	0.245
HAI 0–4/5–6/7–9/10–18, *n*	13/12/3/2	16/13/3/1	29/25/6/3	0.594
HAI score	5.0 (3.0–11.0)	5.0 (1.0–10.0)	5.0 (1.0–11.0)	0.449
F 0–2/3/4/5–6, n	13/4/8/5	11/9/11/2	24/13/19/7	0.971
F score	3.0 (1.0–6.0)	3.0 (0–5.0)	3.0 (0–6.0)	0.810

Values were shown as *n*, *n* (%), or median (range). ALT: Alanine aminotransferase; AFP: Alpha-fetoprotein; APRI: Aspartate aminotransferase-to-platelet ratio index; AST: Aspartate aminotransferase; BMI: Body mass index; F: Ishak F score; FIB-4: Fibrosis 4 score; HAI: Histology activity index; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; PLT: Platelet; qAnti-HBc: Quantitative of anti-hepatitis B virus core antibody; qHBsAg: Quantitative of hepatitis B surface antigen; TBIL: Total bilirubin; ULN: Upper limit of normal.

With follow-up to 78 weeks, 42 (67%) patients achieved a VR, shown as serum HBV DNA <1.30 $\log_{10}$ IU/mL, and 24 patients achieved both serum HBV DNA and HBV RNA undetectable. Details of the efficacy evaluation after 78 weeks of therapy are shown in Supplementary Table 1, https://links.lww.com/CM9/B361. Among the 42 patients who achieved a VR, 15 (36%) were HBeAg positive and 27 (64%) were HBeAg negative. Compared with patients in the non-virological response (NVR) group, patients who achieved a VR had lower levels of HBV RNA (3.72 [1.70–7.42] $\log_{10}$ copies/mL *vs*. 5.15 [1.86–7.87] $\log_{10}$ copies/mL, *P* = 0.001), HBV DNA (5.48 [1.30–8.15] $\log_{10}$ IU/mL vs. 6.17 [3.05–8.66] log™ IU/mL, *P* = 0.013), and quantitative of hepatitis B surface antigen (qHBsAg) (3.37 [1.20–4.57] $\log_{10}$ IU/mL vs. 3.76 [2.50–4.92] $\log_{10}$ IU/mL, *P* = 0.002), as shown in Supplementary Figure 1, https://links.lww.com/CM9/B361. After further dividing the VR

and NVR patients by HBeAg status, both the HBeAg-positive and HBeAg-negative groups had the same trends. Furthermore, we also observed that patients older than 30 years were more likely to achieve a VR (P = 0.008). After 78 weeks of therapy, serum HBV RNA (1.70 [1.70–5.12] $\log_{10}$ copies/mL vs. 4.31 [1.70–6.90] $\log_{10}$ copies/mL, P = 0.002) and qHBsAg (3.26 [0.82–4.12] $\log_{10}$ IU/mL vs. 3.62 [2.37–4.59] $\log_{10}$ IU/mL, P = 0.006) levels were also lower in the VR group than in the NVR group. The proportion of serum HBV RNA below the lower limit of detection after 78 weeks of treatment in the VR and NVR groups was 57% (24/42) and 29% (6/21), respectively, P = 0.034.

Univariate and multivariate analyses were applied to investigate the independent variables associated with the VR to antiviral therapy in the HBeAg-positive and HBeAg-negative patients, respectively [Supplementary Table 2, https://links.lww.com/CM9/B361]. In the HBeAg-positive group, HBV RNA, HBV DNA, and the HAI score were significantly related to the VR at 78 weeks based on the univariate analysis, whereas only the HAI score (P = 0.023) and HBV RNA (P = 0.018) were independent predictors of a VR at 78 weeks based on multivariate analysis. Serum HBV RNA at baseline was not related to the 78-week VR in HBeAg-negative patients.

The area under the receiver operating characteristic (AUROC) curves of serum HBV RNA at baseline for predicting a VR at 78 weeks in HBeAg-positive patients was 0.751 (0.573–0.929), P = 0.019, while the AUROC of the HAI score was 0.756 (0.580–0.931), P = 0.017. The cutoff values of serum HBV RNA and the HAI score at baseline were 4.47 $\log_{10}$ copies/mL (sensitivity = 0.533, specificity = 0.933) and 5.5 (sensitivity = 0.60, specificity = 0.867), respectively.

To our knowledge, this is a unique study since it evaluated the predictive value of HBV RNA in anticipating a VR in normal ALT chronic HBV patients. A considerable number of patients with chronic HBV infection with normal ALT are not currently being treated with antivirals based on the current guidelines. Our results demonstrated that the baseline serum HBV RNA level was an independent non-invasive predictor of VR in HBeAg-positive patients. Unfortunately, no correlation between serum HBV RNA and VR in HBeAg-negative patients was found, which is consistent with Liu *et al*'s report,[4] which revealed that lower initial serum HBV RNA was independently associated with a rapid VR in HBeAg-positive patients. Ji *et al*[5] found that the serum HBV RNA level at week 12 could predict a VR at 96 weeks in HBeAg-positive patients.

The receiver operating characteristic curve analyses and the optimal threshold cutoff value of the serum HBV RNA and HAI score indicated that in chronic hepatitis B (CHB) patients, serum HBV RNA levels below 4.47 log10 copies/mL and HAI scores >5.5 before treatment indicated they were more likely to achieve a VR after 78 weeks of therapy. However, it is challenging to identify patients' HAI scores, as the application of liver biopsy is restricted because of its invasiveness, sampling error, and non-repeatability in the short term. The application prospects of serum HBV RNA as a non-invasive indicator to predict a VR is more extensive.

In conclusion, this study showed that serum HBV RNA was an independent non-invasive indicator to predict a VR in HBeAg-positive patients with normal ALT. Although the number of patients was small and the follow-up time was too short to evaluate HBV RNA drug withdrawal predictor values of long-term nucleos(t)ide analogues therapy, these results will provide a reference for antiviral treatment. Because most normal ALT patients (67%) achieved a VR during therapy, patients who have high levels of HBV RNA (over 4.47 $\log_{10}$ copies/mL) before treatment should be given more attention during treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due

efforts will be made to conceal their identity, but anonymity cannot be guaranteed. This study was approved by The Ethical Committees of Peking University First Hospital (No. 2012-455).

Acknowledgments

The authors gratefully acknowledge the members of the China HepB-Related Fibrosis Assessment Research Group for assisting patient recruitment and data acquisition.

Funding

This work was supported by China Mega-Project for Infectious Diseases (Nos. 2013ZX10002005 and 2017ZX10203202).

Conflicts of interest

None.

References

1. Chinese Society of Infectious Diseases, CMA. Chinese Society of Hepatology, CMA. The guidelines of prevention and treatment for chronic hepatitis B (2019 version) (in Chinese). *Chin J Hepatol* 2019; 27:938–961. doi: 10.3760/cma.j.issn.1007-3418.2019.12.007.

- Cited Here |
- Google Scholar

2. Wu Z, Ma AL, Xie Q, Zhang XQ, Cheng J, Zhang DZ, et al. Significant histological changes and satisfying antiviral efficacy in chronic hepatitis B virus infection patients with normal alanine aminotransferase. Antiviral therapy decision in chronic HBV patients with normal ALT. *Clin Res Hepatol Gastroenterol* 2021; 45:101463doi: 10.1016/j.clinre.2020.05.011.

- Cited Here |
- Google Scholar

3. Huang YW, Takahashi S, Tsuge M, Chen CL, Wang TC, Abe H, et al. On-treatment low serum HBV RNA level predicts initial virological response in chronic hepatitis B patients receiving nucleoside analogue therapy. *Antivir Ther* 2015; 20:369–375. doi: 10.3851/IMP2777.

- Cited Here |
- Google Scholar

4. Liu S, Liu Z, Li W, Zhou B, Liang X, Fan R, et al. Factors associated with the biphasic kinetics of serum HBV RNA in patients with HBeAg-positive chronic hepatitis B treated with nucleos(t)ide analogues. *Aliment Pharmacol Ther* 2020; 52:692–700. doi: 10.1111/apt.15890.

- Cited Here |
- Google Scholar

5. Ji X, Xia M, Zhou B, Liu S, Liao G, Cai S, et al. Serum hepatitis B virus RNA levels predict HBeAg seroconversion and virological response in chronic hepatitis B patients with high viral load treated with nucleos(t) ide analog. *Infect Drug Resist* 2020; 13:1881–1888. doi: 10.2147/IDR.S252994.

- Cited Here |
- Google Scholar

Supplemental Digital Content

- CM9_2022_10_28_ZHAO_CMJ-2021-2480_SDC2.doc; [Word] (520 KB)

Copyright © 2022 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license.

View full article text

^Back to Top

Never Miss an Issue

Get new journal Tables of Contents sent right to your email inbox Type your email

Get New Issue Alerts

Browse Journal Content

- Most Popular
- For Authors
- About the Journal
- Past Issues
- Current Issue
- China Association for Science and Technology
- Chinese Medical Association (Sponsor of CMJ)
- Chinese Medical Association Publishing House
- International Committee of Medical Journal Editors
- National Health Commission
- Register on the website
- Get eTOC Alerts

For Journal Authors

- Submit an article
- How to publish with us

Customer Service

Live Chat

- Browse the help center
- Help
- Contact us at:
  - EMAIL:

cmj@cma.org.cn
- TEL:
86-10-51322179

- Privacy Policy (Updated December 15, 2022)
- Legal Disclaimer
- Terms of Use
- Open Access Policy

- Copyright © 2022
- 京ICP备05052599号-4 The Chinese Medical Association