

How Can We Make Decision for Patients With Chronic Hepatitis B According to Hepatitis B Virus (HBV) DNA Level?

Maryam Keshvari^{1,2}; Seyed Moayed Alavian^{2,3,*}; Heidar Sharafi^{2,3}

¹Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, IR Iran

²Middle East Liver Disease (MELD) Center, Tehran, IR Iran

³Baqiyatallah Research Center for Gastroenterology and Liver Diseases, Baqiyatallah University of Medical Sciences, Tehran, IR Iran

*Corresponding Author: Seyed Moayed Alavian, Baqiyatallah Research Center for Gastroenterology and Liver Diseases, Baqiyatallah University of Medical Sciences, Mollasadra St., Vanak Sq., Tehran, IR Iran. Tel: +98-2188945186, Fax: +98-2188945188, E-mail: editor@hepatmon.com

Received: October 7, 2013; Revised: October 19, 2013; Accepted: October 25, 2013

Background: HBeAg negative hepatitis B infection exerts both inactive carrier state and chronic active hepatitis, which are sometimes difficult to differentiate. Serial hepatitis B virus (HBV) DNA quantification, alanine transaminase (ALT) measurement, and liver histology assessment can help to differentiate these forms of hepatitis B infection.

Objectives: We aimed to clarify the clinical and laboratory characteristics of HBeAg negative hepatitis B patients.

Patients and Methods: Patients with hepatitis B, referred to Tehran Blood Transfusion Hepatitis Clinic from 2011 to 2013, were included and followed for one year. Laboratory assessments including liver function tests, HBV DNA quantification, and liver biopsy (for some cases) were performed.

Results: Two hundred forty-three HBeAg negative hepatitis B patients were stratified into three groups based on to their HBV DNA level including group 1 (G1) with HBV DNA level < 2000 IU/mL, group 2 (G2) with HBV DNA level 2000-20000 IU/mL, and group 3 (G3) with HBV DNA level > 20000 IU/mL. The G2 had more similarity to G1 than G3 regarding their clinical characteristics.

Conclusions: It is concluded that most HBeAg negative hepatitis B patients with serum HBV DNA level of 2000-20000 IU/mL, persistent normal ALT concentration, and no or mild liver damage on biopsy can be clinically managed as HBV inactive carriers.

Keywords: Hepatitis B; Liver Cirrhosis; Viral Load

1. Background

Hepatitis B virus (HBV) infection is a significant health problem. Approximately 350 million persons worldwide are chronically infected with HBV. Patients with chronic HBV infection are at increasing risk of end stage liver disease such as cirrhosis and hepatocellular carcinoma (HCC). According to different studies, 15% to 40% of HBV infected patients develop serious complications of hepatitis B (1, 2). The prevalence of HBV infection in Iran was estimated to be 2.14% (3). All HBV isolates from Iran were genotype D (4, 5). The rate of precore and basal core promoter mutations and progressive liver disease in patients with HBV genotype D infection was found to be more prevalent than HBV infected patients with non-D genotypes (6, 7). Hepatitis B infection consists of few clinical phases including immune tolerance phase, immune clearance phase, and inactive carrier state. Inactive carrier state is characterized by normal alanine transaminase (ALT) concentration, absence of HBeAg and presence of anti-HBeAb, low or undetectable HBV DNA in serum, and

minimal or no histologic changes on liver biopsy. Some patients continue to have moderate levels of HBV replication and active liver disease, but remain to have negative results for HBeAg which most of them have the HBV variants that cannot produce HBeAg due to mutations in the basal core promoter or precore regions (8). According to the last guideline for management of hepatitis B, absence of HBeAg, presence of anti-HBeAb, Serum HBV DNA level < 2000 IU/mL, persistent normal ALT/aspartate transaminase (AST) level, and absence of significant hepatitis on liver biopsy are classified as inactive carrier state. Whereas, HBeAg positivity or serum HBV DNA level > 20000 IU/mL, persistent or intermittent elevation in ALT/AST level, and liver biopsy showing chronic hepatitis with moderate to severe necro-inflammation are classified as chronic active hepatitis B (9). This classification is important since antiviral therapy must be considered just for the patients with chronic active hepatitis presentation. However, differentiation between HBeAg negative chronic active hepatitis B and inactive carrier state is often challenging. We have observed some patients with HBV infection in

Implication for health policy/practice/research/medical education:

2000 IU/mL or 20000 IU/mL, it is the question. While Baseline HBV viral load is one of the main determinants for classification of patients with HBV infection into different forms of disease, there is still disagreement regarding the cutoff value for such application of HBV viral load. In this study, we searched for the appropriate cutoff value and application of HBV viral load to differentiate HBeAg negative chronic active hepatitis B patients from HBV inactive carriers based on their clinical and laboratory assessments.

Copyright © 2014, BRCGL; Published by Kowsar Corp. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

the clinic with normal ALT levels, and HBV DNA levels between 2000 IU/mL and 20000 IU/mL and no or minimal fibrosis on their liver biopsy. Classification of this group of HBV infected patients into chronic active hepatitis or inactive carrier state is a great question.

2. Objectives

The aim of this study was to precise assessment of HBeAg negative hepatitis B infected patients according to their clinical and laboratory features.

3. Patients and Methods

In the current study, a total of 243 treatment naive HBV infected patients referred to Tehran Blood Transfusion Hepatitis Clinic (Tehran, Iran) from 2011 to 2013 were included and followed for one year. HBeAg positive chronic hepatitis B patients and cases with human immunodeficiency and hepatitis C and D antibodies were excluded. Laboratory assessments including liver function tests and HBV DNA quantification (HBV DNA level) were performed for the study population on at least two consecutive patients' samples in a one-year interval. Upper normal limit of ALT was considered 34 IU/L for non-overweight women (BMI of less than 25), and 40 IU/L for non-overweight men (10). HBV DNA level using COBAS TaqMan HBV tests (Roche Diagnostics) and liver biopsy (The results were reported according to the modified Knodell scoring system, as the Ishak score.) was assessed.

On liver histology, liver fibrosis score (stage) ≤ 2 , and liver necro-inflammation score (grade) ≤ 4 were considered as cutoff values to show mild liver damage (11). The liver histology assessment was performed for patients with clinical and laboratory evidence of progressive liver disease, while it was performed optionally for those without such evidence. All study participants provided informed consent, and the study design was approved by appropriate ethics review board. Statistical analysis was performed using SPSS version 20. Categorical variables and continuous variables were analyzed by Fisher exact test and t-test, respectively. P values less than 0.05 were considered to be statistically significant.

4. Results

In the current study, 243 HBeAg negative hepatitis B patients were divided into three groups regarding their HBV DNA level including group1 (G1) with HBV DNA level < 2000 IU/mL, group2 (G2) with HBV DNA level between 2000 IU/mL to 20000 IU/mL, and group3 (G3) with HBV DNA level > 20000 IU/mL. We observed that G2 had more similarity to G1 than G3 (Table 1). There was no statistically significant difference regarding sex, necro-inflammatory score on liver biopsy (grade), and total bilirubin concentration between these groups ($P > 0.05$), but there were significant differences in liver fibrosis (stage), AST, ALT and direct bilirubin mean concentrations between G2 and G3 ($P < 0.05$) (Table 1).

Table 1. Comparison of Demographic and Clinical Characteristics of the Study Population Stratified by HBV DNA

	HBV DNA < 2000 IU/mL (G1) (n = 104)	HBV DNA 2000-20000 IU/mL (G2) (n = 53)	HBV DNA > 20000 IU/mL (G3) (n = 86)	P value G1 vs. G2	P value G2 vs. G3
Age, Mean \pm SD, y	47.4 \pm 12.7	41.8 \pm 12.8	43.5 \pm 13.9	0.01 ^a	0.46 ^a
Sex, No. (%)					
Female	19 (18.3)	16 (30.2)	22 (25.6)	0.11 ^b	0.56 ^b
Male	85 (81.7)	37 (69.8)	64 (74.4)		
Liver Fibrosis, No. (%)					
Mild	16 (94.1)	29 (87.9)	41 (56.2)	0.65 ^b	< 0.01 ^b
Moderate to severe	1 (5.9)	4 (12.1)	32 (43.8)		
Liver Necro-Inflammation, No. (%)					
Mild	12 (80.0)	14 (48.3)	30 (42.3)	0.06 ^b	0.66 ^b
Moderate to severe	3 (20.0)	15 (51.7)	41 (57.7)		
ALT^c, Mean \pm SD, IU/L	40.3 \pm 28.7	40.5 \pm 27.0	68.5 \pm 53.1	0.98 ^a	< 0.01 ^a
AST^c, Mean \pm SD, IU/L	29.7 \pm 17.1	32.1 \pm 18.6	46.9 \pm 26.5	0.42 ^a	< 0.01 ^a
Direct bilirubin, Mean \pm SD, mg/dL	0.23 \pm 0.14	0.31 \pm 0.19	0.42 \pm 0.39	< 0.01 ^a	0.03 ^a
Total bilirubin, Mean \pm SD, mg/dL	0.92 \pm 0.54	1.08 \pm 0.58	1.24 \pm 0.89	0.10 ^a	0.26 ^a

^a t-test.

^b Fisher exact test.

^c Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.

5. Discussion

A previous study showed that HBV DNA level more than 20000 IU/mL can be considered as a cutoff value to differentiate patients with HBeAg negative chronic active hepatitis B and those in an inactive carrier state (12). However, another study proposed that due to the fluctuation in HBV DNA level among HBeAg negative chronic hepatitis B patients, there is no absolute cutoff value reliable to differentiate HBeAg negative chronic active hepatitis B patients and hepatitis B inactive carriers (13). Another study confirmed that ALT \leq 30 IU/L and HBV DNA load \leq 20000 IU/mL had high sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to differentiate HBV inactive carriers and HBeAg negative chronic active hepatitis B (14). In a cohort of Alaska natives, among HBeAg negative hepatitis B patients, 25% met the criteria for chronic active HBV infection. The patients had mild histologic liver changes, if HBV DNA level never exceed 20000 IU/mL during the follow up period (15). A study from Greece showed that histologically significant liver disease was rare in patients with HBV infection with persistent normal liver enzymes, and HBV DNA \leq 20000 IU/mL, so these patients could be considered as true inactive HBV carriers (16). On the other hand, in different studies, HBV DNA level of 2000 IU/mL was considered to differentiate inactive carriers and HBeAg negative chronic hepatitis B (17, 18). However HBV DNA level can fluctuate to lower than 2000 IU/mL in patients with HBeAg negative chronic hepatitis B, and as a result HBV clinical state can be misclassified based on a single HBV DNA level, so appropriate follow-up by HBV DNA and ALT levels is recommended to differentiate inactive carriers and patients with HBeAg negative chronic hepatitis B (18). One of our study limitations was its proportionally small number of patients with HBV DNA level 2000 IU/mL to 20000 IU/mL. We propose a longitudinal study with larger sample size to seek the outcome of this group of patients.

In conclusion, it seems that patients with HBV infection should be followed regularly with ALT and HBV DNA levels assessment. The current study, demonstrated that most HBeAg negative hepatitis B patients with serum HBV DNA level between 2000 IU/mL to 20000 IU/mL, persistent normal ALT concentration, and no or mild liver damage on biopsy could be considered as HBV inactive carriers.

Acknowledgements

We are grateful to the staff of Hepatitis Clinic of Tehran Blood Transfusion Center, and the Middle East Liver Disease (MELD) Center.

Authors' Contribution

All authors equally contributed in the study design, data collection, and manuscript preparation.

Financial Disclosure

Authors declared no financial disclosure regarding this study.

Funding/Support

This study had no funding source.

References

- Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology*. 2007;**45**(2):507-39.
- Aspinall EJ, Hawkins G, Fraser A, Hutchinson SJ, Goldberg D. Hepatitis B prevention, diagnosis, treatment and care: a review. *Occup Med (Lond)*. 2011;**61**(8):531-40.
- Alavian SM, Hajarizadeh B, Ahmadvad-Asl M, Kabir A, Bagheri-Lankarani K. Hepatitis B Virus infection in Iran: A systematic review. *Hepat Mon*. 2008;**8**(4):281-94.
- Eftekhari Y, Kazemi Arababadi M, Hakimi H, Rezazadeh Zarandi E. Common HBV genotype in southeastern Iranian patients. *Arch Iranian Med*. 2010;**13**(2):147-9.
- Garmiri P, Rezvan H, Abolghasemi H, Allain JP. Full genome characterization of hepatitis B virus strains from blood donors in Iran. *J Med Virol*. 2011;**83**(6):948-52.
- Malmstrom S, Eilard A, Larsson SB, Hannoun C, Norkrans G, Lindh M. Genotype impact on long-term virological outcome of chronic hepatitis B virus infection. *J Clin Virol*. 2012;**54**(4):321-6.
- Shi YH. Correlation between hepatitis B virus genotypes and clinical outcomes. *Jpn J Infect Dis*. 2012;**65**(6):476-82.
- McMahon BJ. Epidemiology and natural history of hepatitis B. *Semin Liver Dis*. 2005;**25** Suppl 1:3-8.
- Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;**50**(3):661-2.
- Mohamadnejad M, Pourshams A, Malekzadeh R, Mohamadkhani A, Rajabiani A, Asgari AA, et al. Healthy ranges of serum alanine aminotransferase levels in Iranian blood donors. *World J Gastroenterol*. 2003;**9**(10):2322-4.
- Fateen AA, Shahin RY, Farres MN, Eldeeb MA, Amer HA. Assessment of hepatic fibrosis and necroinflammation among inactive HBsAg carriers in Egypt. *Ann Hepatol*. 2012;**11**(4):464-70.
- Chu CJ, Hussain M, Lok AS. Quantitative serum HBV DNA levels during different stages of chronic hepatitis B infection. *Hepatology*. 2002;**36**(6):1408-15.
- Martinot-Peignoux M, Boyer N, Colombat M, Akreimi R, Pham BN, Ollivier S, et al. Serum hepatitis B virus DNA levels and liver histology in inactive HBsAg carriers. *J Hepatol*. 2002;**36**(4):543-6.
- Ijaz B, Ahmad W, Javed FT, Gull S, Hassan S. Revised cutoff values of ALT and HBV DNA level can better differentiate HBeAg (-) chronic inactive HBV patients from active carriers. *Virology*. 2011;**8**:86.
- McMahon BJ, Bulkow L, Simons B, Zhang Y, Negus S, Homan C, et al. Relationship Between Level of HBV DNA and Liver Disease - a Population-Based Study of Hepatitis B e Antigen-Negative Persons with Hepatitis B. *Clin Gastroenterol Hepatol*. 2013.
- Papatheodoridis GV, Manolakopoulos S, Liaw YF, Lok A. Follow-up and indications for liver biopsy in HBeAg-negative chronic hepatitis B virus infection with persistently normal ALT: a systematic review. *J Hepatol*. 2012;**57**(1):196-202.
- Zacharakis G, Koskinas J, Kotsiou S, Tzara F, Vafeiadis N, Papoutselis M, et al. The role of serial measurement of serum HBV DNA levels in patients with chronic HBeAg(-) hepatitis B infection: association with liver disease progression. A prospective cohort study. *J Hepatol*. 2008;**49**(6):884-91.
- Sorrell MF, Belongia EA, Costa J, Gareen IF, Grem JL, Inadomi JM, et al. National Institutes of Health consensus development conference statement: management of hepatitis B. *Hepatology*. 2009;**49**(5 Suppl):S4-S12.