ORIGINAL ARTICLE

Evaluation of HBsAg Seroclearance in Patients with Hepatitis B

Mehmet Can Taşkın[1], Ahmet Uyanikoglu[2], Cigdem Cindoglu[3]

Abstract

Objective: Hepatitis B surface antigen (HBsAg) seroclearance/seroconversion is regarded as an indicator of the ultimate immune control of hepatitis B virus (HBV) infections. HBsAg loss is the most important endpoint, as it shows deep suppression of HBV replication and viral protein expression. This study was aimed to retrospectively evaluate the HBsAg seroclearance/seroconversion status in patients with acute or chronic hepatitis B (CHB) diagnosis.

Materials and methods: Patients diagnosed with acute or CHB at the Harran University Faculty of Medicine Department of Gastroenterology between January 2012 and December 2020 were included in this study. This study was designed as a retrospective historical cohort. Experimental analysis of the data was done with the help of the SPSS version 22.0 package program.

Results: Of 1,053 patients with positive HBsAg, 854 patients with sufficient data in their files were included in this study. There were 494 (57.8%) males and 360 (42.2%) females; the mean age was 42.71 ± 14.31 (range 18–88). The mean duration of illness was 86.13 ± 72.92 months. In the 9-year follow-up of 854 patients, 65 (7.9%) of the last HBsAg test were negative and seroclearance had developed. The last anti-HBs test was positive in 49 (75.4%) of 65 patients who developed seroclearance, and it was found that seroconversion had developed. Twenty-seven of 30 (90%) of the patients who developed seroclearance had liver transplantation. Sixteen of 19 (84.2%) of them had acute hepatitis B, 14 of 477 (2.9%) were hepatitis carriers, 5 of 201 (2.5%) had e-negative CHB, 2 of 36 (5.6%) had cirrhosis, and 1 of 43 (2.3%) of them were delta hepatitis who developed seroclearance disease; none of the 38 e-positive CHB patients developed seroclearance.

Conclusion: In the 9-year follow-up of patients who were positive for HBsAg at their first admission, approximately one-tenth (7.9%) developed seroclearance, and two-thirds also developed seroconversion. After liver transplantation and acute hepatitis B, almost all patients developed seroclearance, whereas, in approximately 3% of carriers (e-negative CHB and cirrhotic patients) seroclearance developed.

Keywords: Chronic hepatitis B infection, HBsAg seroclearance/seroconversion.

Euroasian Journal of Hepato-Gastroenterology (2022): 10.5005/jp-journals-10018-1352

Introduction

The hepatitis B virus (HBV) infection can cause subclinical or asymptomatic infection, acute self-limiting hepatitis, or fulminant hepatitis requiring liver transplantation. People infected with chronic hepatitis B (CHB) may also develop cirrhosis or hepatocellular carcinoma (HCC).[1] It is estimated that more than 350 million people worldwide are infected with CHB, resulting in 600,000 deaths each year from cirrhosis and HCC. Because more than 90% of infected newborns will develop CHB, eradication efforts have focused on universal vaccination and screening for those born in endemic areas.[2] Turkey is among the moderately endemic regions in terms of HBV frequency. Hepatitis B surface antigen (HBsAg) positivity is 3.9%, and it is estimated that close to 3 million people are infected with HBV. In countries with intermediate endemics, such as Turkey, the frequency of hepatitis B infection varies between 2 and 8%.[3]

It is widely accepted that HBsAg clearance is associated with better clinical outcomes. Studies have shown that the annual rate of HBsAg loss is approximately 0.5–2.3%, depending on age at enrollment and status of liver disease.[4]

The main goal of treatment for patients with CHB infection is to improve survival and quality of life by preventing disease progression and ultimately the development of HCC. Additional goals of antiviral therapy are the prevention and treatment of mother-to-child transmission, hepatitis B reactivation, and HBV-related extrahepatic manifestations. HBsAg loss is considered the optimal treatment endpoint, termed functional therapy, but is rarely achieved with current antiviral therapy.[5]

[1]Department of Internal Medicine, Sanliurfa Balikligol State Hospital, Sanliurfa, Turkey

[2]Department of Gastroenterology, Harran University, Sanliurfa, Turkey

[3]Department of Internal Medicine, Harran University, Sanliurfa, Turkey

Corresponding Author: Cigdem Cindoglu, Department of Internal Medicine, Harran University, Sanliurfa, Turkey, Phone: +5052281375, e-mail: ccindoglu@gmail.com

How to cite this article: Taşkın MC, Uyanikoglu A, Cindoglu C. Evaluation of HBsAg Seroclearance in Patients with Hepatitis B. Euroasian J Hepato-Gastroenterol 2022;12(2):65–68.

Source of support: Nil

Conflict of interest: None

This study aimed to evaluate HBsAg seroclearance and seroconversion status after spontaneous or antiviral therapy, in patients diagnosed with acute or CHB.

Materials and Methods

In this study, the data of patients who were found to be positive for HBsAg between January 2012 and December 2020 at the xxx University, Faculty of Medicine, Department of Gastroenterology were analyzed retrospectively. Our research is a single-center historical cohort study. It was made with the permission of the Harran University, Faculty of Medicine Ethics Committee, numbered E.21890 and dated June 16, 2020.

Inclusion and Exclusion Criteria

The inclusion criteria were to be older than 18 years of age and to have serum HBsAg and anti-HBs levels measured at admission.

The files of the patients who met the inclusion criteria were reviewed retrospectively, and demographic characteristics such as age and gender at the time of admission, HBsAg, anti-HBs, HBeAg, anti-HBe levels, HBV DNA level, and liver function tests were evaluated, and HBsAg seroclearance and seroconversion status were analyzed in long-term follow-ups.

Methods Used in HBV DNA Measurement

HBV DNA level was measured at the Harran University Medical Faculty Medical Microbiology Laboratory with the Abbott m2000 RT device using the polymerase chain reaction (PCR) method. Its unit is measured in IU/mL. Those with HBV DNA levels below 10 IU/mL were considered negative.

Methods Used in Measuring HBsAg, Anti-HBs, HBeAg, and Anti-HBe

Levels were measured using the ELISA method with the Abbott I2000 device in the Medical Microbiology Laboratory of the Medical Faculty of Harran University. Its unit is measured as S/CO. HBsAg range of 0–1 was considered negative, and >1 was considered positive. Anti-HBs range of 0–10 was considered negative, and >10 was considered positive.

Methods Used to Measure ALT-AST-GGT-ALP

Levels were measured with the Abbott 16000 Architect device in the Medical Biochemistry Laboratory of the Medical Faculty of Harran University. The reference range of alanine aminotransferase (ALT) level is 0–55, and its unit is measured as U/L. The reference range of aspartate aminotransferase (AST) level is 5–34, and its unit is measured as U/L. The reference range of gamma-glutamyl transferase (GGT) level is 9–36, and its unit is measured as IU/L. The reference range of alkaline phosphatase (ALP) level is 46–113, and its unit is measured as U/L.

Statistical Method

The data were transferred to the SPSS statistical database. Statistical Package for Social Sciences Version (SPSS) 20.0 program was used for statistics. Frequency and crosstab tests were used for the frequency analysis of the data.

Results

Of the 1,053 patients who were found to be HBsAg positive at the first admission, 854 patients with sufficient data in their files were included in this study. Of the 854 patients, 494 (57.8%) were male and 360 (42.2%) were female, with a mean age of 42.71 ± 14.31 (range 18–88). The mean disease duration was 86.13 ± 72.92 months.

Nineteen patients (2.2%) were acute hepatitis, 477 patients (55.9%) were carriers of inactive hepatitis B, 201 patients (23.5%) had e-negative CHB, 48 patients (5.6%) had e-positive CHB, 36 patients (4.2%) had HBV-related cirrhosis, and 43 patients (5.1%) had delta hepatitis. Cirrhosis developed in 6 (14%) of 43 delta hepatitis patients. Thirty patients (3.5%) had liver transplantation. Of these 30 patients, 9 had delta hepatitis. The clinical distribution of the cases is shown in Table 1.

Of 854 patients who had a positive initial HBsAg test, 65 (7.6%) had a negative final HBsAg test and had seroclearance, while 789 (92.4%) had a positive HBsAg test.

Table 1: The clinical distribution of the cases

Clinic	*n*	*(%)*
Acute hepatitis B	19	2.2%
Inactive hepatitis B	477	55.9%
e(–) chronic hepatitis B	201	23.5%
e(+) chronic hepatitis B	48	5.6%
Cirrhosis	36	4.2%
Liver transplantation	30	3.5%
Delta hepatitis	43	5.1%
	854	100%

Table 2: The clinical distribution of patients who developed seroclearance and seroconversion

Clinic	*n*	*Seroclearance n (%)*	*Seroconversion n (%)*
Acute hepatitis B	19	16 (84.2%)	12 (63.2%)
Inactive hepatitis B	477	14 (2.9%)	8 (1.6%)
e(–) chronic hepatitis B	201	5 (2.5%)	4 (1.9%)
e(+) chronic hepatitis B	48	0	0
Cirrhosis	36	2 (5.6%)	0
Liver transplantation	30	27 (90%)	25 (83.3%)
Delta hepatitis	43	1 (2.3%)	0
	854	65 (100%)	49 (100%)

The last anti-HBs test was positive in 49 (5.7%) of 854 patients whose initial anti-HBs tests were negative. Anti-HBs test was still negative in 805 patients (94.3%). Seroconversion developed in 49 (75%) of 65 patients who became HBsAg negative. The clinical distribution of patients who developed seroclearance and seroconversion is shown in Table 2.

Of the 854 patients, 769 had initial HBeAg results. HBeAg test was negative in 696 (90.5%) of these patients and positive in 73 (9.5%). HBeAg turned negative and anti-HBe seroconversion developed in 48 (65.8%) of 73 positive patients whose follow-up results were available.

Of 854 patients, 358 (42%) received various treatments. Of 358 patients, 186 (52%) were on tenofovir, 79 (22.1%) were on entecavir, 24 (6.7%) were on lamivudine, and 69 (19.2%) were on pegylated interferon (peg-IFN) 2a/2b treatment. Of 40 patients who developed seroclearance with treatment, 26/186 were treated with tenofovir, 10/79 with entecavir, and 4/24 with lamivudine. Thirty of these 40 patients were liver transplant patients. Of the 30 patients who had liver transplantation, 22 (73.3%) were receiving tenofovir, 7 (23.3%) entecavir, and 1 (3.4%) lamivudine.

Excluding liver transplant patients, 4 out of 328 treated patients (2.4%) received tenofovir treatment, 3 (4.1%) of 72 patients were treated with entecavir, and 3 (13%) of 23 patients were treated with lamivudine, and seroclearance had improved. A total of 69 patients who received peg-IFN 2a and peg-IFN 2b treatment did not develop seroclearance (Table 3).

Of 854 HBsAg-positive patients at the first admission, 358 (41.9%) received treatment and 496 (58.1%) did not receive treatment. Of the 358 patients who received treatment, 132 had final HBV DNA. One hundred and eighteen (89.4%) of 132 patients

Table 3: The treatment received by the patients and the distribution of seroclearance development

Treatment	*(n = 328)*	*Seroclearance n (%)*
Tenofovir	164	4 (2.4%)
Entecavir	72	3 (4.1%)
Lamivudine	23	3 (13%)
Peg-IFN 2a	66	0 (0%)
Peg-IFN 2b	3	0 (0%)

Except for 30 patients who underwent liver transplant

were HBV DNA negative. Initial AST levels of the patients were 95.24 ± 283.23, ALT levels were 118.31 ± 350.61, GGT levels were 49.31 ± 72.18, and ALP levels were 100.98 ± 202.68.

Discussion

It is estimated that more than 350 million people worldwide are infected with CHB, resulting in 600,000 deaths each year from cirrhosis and HCC.[2] Turkey is among the moderately endemic regions in terms of HBV frequency, and it is estimated that nearly 3 million people are infected with HBV.[3] It is widely accepted that HBsAg clearance is associated with better clinical outcomes. Studies have shown that the annual rate of HBsAg loss is between 0.5 and 2.3%, depending on the age of enrollment and the status of liver disease.[4] This study was aimed to retrospectively investigate the main HBsAg seroclearance and seroconversion rates and other clinical features in HBsAg-positive patients who were followed up with for about 9 years.

HBsAg loss is the most important endpoint, as it shows a profound suppression of HBV replication and viral protein expression. Liaw et al., in their study of 1965 patients in Taiwan, showed that HBsAg seroclearance occurred at an average rate of 1.15% per year. The cumulative probability of HBsAg seroclearance is 8.1% after 10 years but increased disproportionately to 24.9% and 44.7% at 20 and 25 years' follow-up, respectively. These data suggest that HBsAg seroclearance may accelerate with longer (>10 years') follow-up.[6] In our study, 65 (7.9%) of 854 patients had a negative final HBsAg test during their 9-year follow-up, and had seroclearance developed. Our results showed that HBsAg seroclearance developed at a rate similar to this study in approximately 9 years of follow-up.

In the same study, only 17% of patients had detectable anti-HBs within 1 year after HBsAg seroclearance, while this rate increased to 56% at the 5th year and 76% at the 10th years.[7] Similarly, in our study, 49 of 65 patients (75%) had a positive final anti-HBs test and seroconversion was observed.

In the seroprevalence study conducted by Tozun et al. in 2015, 41% of HBsAg-positive patients were female and 59% were male.[3] Similarly, there was a slight male dominance in our study, 494 (57.8%) of the patients were male and 360 (42.2%) were female, with a mean age of 42.71 ± 14.31 years.

Fung et al.'s HBsAg seroclearance rates after 8 years of follow-up with entecavir monotherapy on 265 post-transplantation patients were 90% at 1 year and 95% at 5 years. At 1 year post-transplant, 95% had undetectable HBV DNA, reaching almost 100% at 2 years.[8] In our study, HBsAg seroclearance was developed in 28/30 patients with liver transplantation.

The probability of progression from acute hepatitis B to CHB, according to the period in which HBV was taken, has been reported to be approximately 90% in the perinatal period, 20–50% between the ages of 1–5, and 5% in the adult age. Improvement is observed in approximately 95% of adult patients.[6] In our study, the last HBsAg test was negative in 16 (84.2%) of 19 patients diagnosed with acute hepatitis. Our results were similar to the literature rates.

In a retrospective study of 4061 HBsAg-positive patients, it was reported that spontaneous HBsAg seroclearance occurred in a total of 47 patients (1.2%), namely, 24 asymptomatic carriers, 7 chronic hepatitis patients, 7 cirrhosis patients, and 9 HCC patients. In this study, 7 (14.9%) of 47 seroclearance were diagnosed with cirrhosis and 7 (14.9%) with CHB.[9] Compared to this series, our seroclearance rate was higher (7.9%), which may be related to the follow-up period. In our study, of 65 patients who developed seroclearance, 14 (2.9%) were inactive carriers, 5 (2.5%) had chronic hepatitis, and 2 (3.1%) had cirrhosis.

Although rare, spontaneous HBsAg clearance may occur in inactive HBsAg carriers. In previous publications, it has been reported that it is seen between 0.5 and 2% per year in Western societies and 0.05 and 0.8% per year in Asian countries.[10–12] In our study, spontaneous seroclearance developed in 14 (2.9%) of 477 HBsAg carrier patients during a 9-year follow-up.

In the study of Woo et al. with tenofovir and entecavir, virological response with tenofovir was 88%, HBeAg seroconversion was 20%, and HBsAg loss was 5% in HBeAg-positive patients after 1 year of treatment. With entecavir, the virological response was found to be 61% and HBsAg loss was 1%.[13] In the study conducted by Marcellin et al. on the 5-year treatment results of patients receiving tenofovir, the virological response rate was 97% in HBeAg-positive patients and 99% with a 40% HBeAg seroconversion in HBeAg-negative patients.[7] In our study, 118 (89.4%) of 132 patients who received tenofovir, entecavir, and lamivudine treatment, and whose data could be accessed, were negative for HBV DNA. Our study results were similar to the existing studies.

In the study of Kwon et al., when the response rates of the patients after 1-year follow-ups were examined, HBsAg seroconversion was not seen in the lamivudine and telbivudine groups, and it was found at 3 and 2% for tenofovir and entecavir.[14] In our study, excluding transplant patients, 4 of 164 (2.4%) patients were treated with tenofovir, 3 (4.1%) of 72 patients were treated with entecavir, and 3 (13%) of 23 patients were treated with lamivudine. Seroclearance had improved. Dienstag et al. reported that 23% of 40 patients with HBeAg seroconversion who received lamivudine lost HBsAg after a median period of 36 months.[15] Our seroconversion rates with tenofovir and entecavir were similar and close to the literature, and a higher rate of HBsAg seroclearance was obtained with lamivudine. It was thought that this might be due to the relatively small number of patients, the fact that lamivudine patients received longer treatment, and possible interferon use before.

The limitations of this study are that this study, which was carried out in patients followed up with a diagnosis of HBV infection, was conducted retrospectively, with inaccessible data and an insufficient number of patients for some groups.

HBsAg loss is considered the optimal treatment endpoint, termed "functional therapy," but it is rarely achieved with the current antiviral therapy. The main goal in all treatment options is to provide long-term suppression of the HBV DNA level. It has been shown that when HBV DNA suppression is provided, the progression of fibrosis stops or even improves, and the risk of HCC decreases. In HBeAg-positive individuals, anti-HBe seroconversion is often a valuable endpoint, as it represents a partial immune control of chronic HBV infection. ALT normalization is a good indicator of suppression of necroinflammation, especially in the liver. It has been shown that the inhibition of viral

replication by antiviral therapy provides an elimination of chronic HBV-induced necroinflammatory activity and progressive fibrotic liver processes in the vast majority of patients, which in turn reduces the risk of HCC.[16–19] In this study, besides HBsAg seroclearance and seroconversion, HBeAg seroconversion and suppression of HBV DNA were also investigated.

As a result, in patients with hepatitis B, which is an important health problem in our country and our region, seroclearance developed in approximately one-tenth (7.9%) of patients, and seroconversion developed in two-thirds of the patients who were positive for HBsAg at their first application, in an average of 9 years of follow-up. After liver transplantation and acute hepatitis B, seroclearance developed in almost all patients, while seroclearance developed in approximately 3% of carriers, e-negative CHB patients, and cirrhotic patients. The data obtained are generally similar to the literature data, and with this study, important data were obtained, especially in terms of seroclearance/seroconversion, regarding hepatitis B patients in the Sanliurfa region, showing that this disease should be followed closely and regularly.

Orcid

Mehmet Can Taşkın https://orcid.org/0000-0002-3183-3609

References

1. Shepard CW. Hepatitis B virus infection: epidemiology and vaccination. Epidemiol Rev 2006;28:112–125. DOI: 10.1093/epirev/mxj009.
2. Tujios SR, Lee WM. New advances in chronic hepatitis B. Curr Opin Gastroenterol 2012;28:193–197. DOI: 10.1097/MOG.0b013e32835297ef.
3. Tozun N, Ozdogan O, Cakaloglu Y, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a field-work TURHEP study. Clin Microbiol Infect 2015;21:1020–1026. DOI: 10.1016/j.cmi.2015.06.028.
4. Tseng TC, Liu CJ, Yang HC, et al. Determinants of spontaneous surface antigen loss in hepatitis B e antigen-negative patients with a low viral load. Hepatology 2012;55:68–76. DOI: 10.1002/hep.24615.
5. Lampertico P, Agarwal K, Berg T, et al. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–398. DOI: 10.1016/j.jhep.2017.03.021.
6. Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009;373:582–592. DOI: 10.1016/S0140-6736(09)60207-5.
7. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013;381:468–475. DOI: 10.1016/S0140-6736(12)61425-1.
8. Fung J, Wong T, Chok K, et al. Long-term outcomes of entecavir monotherapy for chronic hepatitis B after liver transplantation: results up to 8 years. Hepatology 2017;66:1036–1044. DOI: 10.1002/hep.29191.
9. Amagai M, Matsushima K. Overview on autoimmunity and autoinflammation. Inflamm Regener 2011;31:50–51. DOI: 10.2492/inflammregen.31.50.
10. Liaw YF, Sheen IS, Chen TJ, et al. Incidence, determinants and significance of delayed clearance of serum HBsAg in chronic hepatitis B virus infection: a prospective study. Hepatology 1991;13:627–631. DOI: 10.1002/hep.1840130403.
11. Lok A. Chronic hepatitis B. Hepatology 2001;34:1225–1241. DOI: 10.1053/jhep.2001.29401.
12. Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis 2003;23:47–58. DOI: 10.1055/s-2003-37590.
13. Woo G, Tomlinson G, Nishikawa Y, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology 2010;139:1218–1229.e5. DOI: 10.1053/j.gastro.2010.06.042.
14. Kwon H, Lok AS. Hepatitis B therapy. Nat Rev Gastroenterol Hepatol 2011;8:275–284. DOI: 10.1038/nrgastro.2011.33.
15. Dienstag JL, Cianciara J, Karayalcin S, et al. Durability of serologic response after lamivudine treatment of chronic hepatitis B. Hepatology 2003;37:748–755. DOI: 10.1053/jhep.2003.50117.
16. Uyanikoglu A. Chronic hepatitis B infection. J Infect Dis Ther 2014;02. DOI: 10.4172/2332-0877.1000133.
17. Papatheodoridis G, Chan HLY, Hansen BE, et al. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. J Hepatol 2015;62:956–967. DOI: 10.1016/j.jhep.2015.01.002.
18. Su TH, Hu TH, Chen CY, et al. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. Liver Int 2016;36:1755–1764. DOI: 10.1111/liv.13253.
19. Kim GA, Lim YS, An J, et al. HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. Gut 2014;63:1325–1332. DOI: 10.1136/gutjnl-2013-305517.