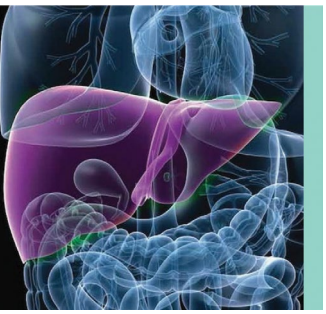

Life After s Loss: Impact of Hepatitis B s Antigen Loss on Future Patient Outcomes

Daniel Q. Huang, M.D., [*,†] *and Seng Gee Lim, M.D.* [*,†]

Chronic hepatitis B (CHB) affects an estimated 257 million people worldwide and contributed to 887,000 deaths in 2015 alone.[1] Hepatitis B s antigen (HBsAg) is present in 3.6% of the world's population,[2] and 12% to 20% of patients with CHB go on to experience development of liver cirrhosis. Among the individuals with cirrhosis, 20% to 23% experience development of liver decompensation, and 6% to 15% experience development of hepatocellular carcinoma (HCC).[3]

The presence of covalently closed circular DNA and hepatitis B virus (HBV) integration into DNA makes complete removal of HBV unlikely with current antiviral strategies. An international workshop involving European Association for the Study of the Liver and American Association for the Study of Liver Diseases concluded that functional cure, or HBsAg loss 6 months after stopping therapy, is an acceptable goal of therapy.[4]

FREQUENCY OF HBSAG LOSS

A large systematic review and meta-analysis of 42,588 treated and untreated individuals with cohorts from Asia, Europe, and America demonstrated an overall HBsAg seroclearance rate of 1% (pooled annual rate) (95% confidence interval [CI]: 0.79-1.27).[5] After 15 years, the cumulative rate of HBsAg seroclearance increased to 18%. This meta-analysis did not find any statistical significance in the annual rate of HBsAg seroclearance between treated (0.8%) and untreated (1.3%) individuals, although there was a higher rate of HBsAg loss among individuals treated with interferon (IFN) compared with nucleos(t)ide analogues (NUCs). Individuals who were HBeAg negative, with lower baseline HBV DNA and quantitative HBsAg levels, had higher rates of HBsAg seroclearance, suggesting that more patients in the inactive carrier phase achieve functional cure. Similarly, a separate

Abbreviations: CHB, chronic hepatitis B; CI, confidence interval; HBsAg, hepatitis B s antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN, interferon; NUC, nucleos(t)ide analogue; qHBsAg, quantitative hepatitis B s antigen.

From the *Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore; and †Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

Potential conflict of interest: S.G.L. advises and received grants from Gilead, Abbott, and Roche. He advises AbbVie, Springbank, Kaleido Biosciences, and Arbutus. He received grants from Fibronostics and Merck.

Received January 27, 2020; accepted May 16, 2020.

View this article online at wileyonlinelibrary.com

meta-analysis in untreated individuals also reported a HBsAg loss rate of 1% a year.[6]

DISCONTINUING NUCs AS A STRATEGY TO INCREASE HBsAg LOSS

There has been considerable interest in stopping NUCs as a strategy to achieve HBsAg loss. This was first noted in a study by Hadziyannis et al.,[7] who followed 33 HBeAg-negative patients with undetectable HBV DNA and stopped adefovir. Eighteen patients achieved sustained response (HBV DNA < 2000 IU/mL and normal alanine aminotransferase), with 13 of them losing HBsAg after a follow-up period of 5.5 years. In contrast, 15 patients were restarted with NUCs, and only 1 lost HBsAg. Subsequently, a number of studies have attempted to explore HBsAg loss by stopping NUCs with mixed results, some achieving 46.7% HBsAg loss,[8] whereas others achieved only a low rate of 2%[9] or even no HBsAg loss.[10] The heterogeneity in HBsAg loss rates is clearly due to multiple factors, such as duration of antiviral therapy, HBeAg status, duration of follow-up after stopping NUCs, and the quantitative HBsAg (qHBsAg) level at the time of treatment discontinuation. A systematic review reported that a HBsAg level <100 IU/mL prior to stopping NUCs is a useful marker for identifying patients who could potentially stop therapy.[11] Papatheodoridis et al.[12] conducted a systematic review evaluating studies that discontinued NUCs when patients were in viral remission. The pooled estimate of HBsAg loss was 2%. This meta-analysis involved multiple studies with heterogenous study designs, and the follow-up may not have been long enough to address this question.

RISK FOR LIVER-RELATED COMPLICATIONS AFTER HBsAg LOSS

Overall Risk for Complications

Due to the variability in studies that examined clinical outcomes after HBsAg loss, the highest quality data come from meta-analyses with low risk for bias. Such a meta-analysis has been presented at the European Association for the Study of the Liver by Choi et al. from the HBV Forum.[13] The authors included 25 studies, with almost 1.4 million person-years of follow-up from 178,000 patients. A total of 33,000 of these individuals experienced s antigen seroclearance. Only studies with more than 50 patients and at least 2 years of follow-up were included. The pooled rate ratio for the first reported adverse clinical event (a composite of decompensation, HCC, need for liver transplantation, or death) was 0.34 (95% CI: 0.23-0.50, $P < 0.001$). When only studies that evaluated treated patients were included, there were no significant differences in the rate ratios for the composite outcome between treatment types (IFN, NUC, or IFN and NUC; $P = 0.30$). There was also no significant difference in the rate ratios between the treated and untreated groups. Subgroup analysis evaluating the effect of genotype, presence of coinfection, length of follow-up, and baseline HBeAg status did not show a significant difference in the rate ratios for the composite outcome. The authors checked for confounders by performing a meta-regression evaluating the effect of years of follow-up, publication year, and journal impact factor on the primary endpoint. None of these factors were significant.

Risk for Development of Decompensation

In the earlier-mentioned systematic review and meta-analysis, Choi et al.[13] reported that five studies provided data for the risk for decompensation after HBsAg loss. The pooled relative rate for decompensation was 0.31 (95% CI: 0.15-0.64, $P = 0.002$).

Risk for Development of HCC

Choi et al.[13] reported that the pooled rate ratio for HCC development in patients who had HBsAg loss was 0.31 (95% CI: 0.21-0.44, $P < 0.001$). This pooled estimate was derived from an analysis of 22 studies. The pooled estimate for HCC development was highly significant and mirrored the pooled estimate from the meta-analyses for the first reported adverse clinical event.

Mortality and Need for Liver Transplantation

HBsAg loss has been shown to improve survival in multiple studies. Among patients without cirrhosis with HBsAg loss, only 1/189 patients passed away in a Taiwanese cohort during follow-up, and 0/164 patients died in a Japanese cohort with median follow-up of more than 5 years.[14,15] In contrast, patients with cirrhosis prior to developing HBsAg loss had a higher mortality, with 1/29 and 2/32 patients in a Taiwanese and European cohort, respectively, passing away over more than 4 years of mean follow-up, suggesting that the presence of cirrhosis in HBsAg loss makes a difference in overall outcome.[14,16]

Choi et al.[13] reported a pooled rate ratio of 0.75 (95% CI: 0.57-0.99, $P = 0.043$) for a composite secondary

endpoint of death or liver transplant in individuals who underwent HBsAg loss, implying an average survival benefit or avoiding liver transplant in 25% of patients who achieve HBsAg loss.

HEPATIC STEATOSIS AND HBsAg SEROCONVERSION

There has been debate about whether hepatic steatosis affects HBsAg seroconversion rates. Some authors have hypothesized that hepatic steatosis may interfere with the cytoplasmic distribution of HBsAg and induction of hepatocyte apoptosis. In a Taiwanese study involving 155 patients with HBsAg seroconversion, these authors observed that those with steatosis achieved HBsAg seroconversion at a younger age (49 versus 53 years, $P = 0.001$).[17] The same authors also performed a case-control study comparing HBsAg seroconverters matched against nonseroconverters, and concluded that moderate-to-severe hepatic steatosis was significantly more prevalent in patients with HBsAg seroconversion.[18] Intrahepatic HBsAg-positive immunostaining was noted to be decreased in patients with hepatic steatosis.[19] However, the available evidence is still inconclusive, and further well-designed studies are required.

FACTORS THAT AFFECT HCC RISK AFTER HBsAg SEROCONVERSION

Liu et al.[20] performed a systematic review and meta-analyses involving 28 studies and 34,952 patients to evaluate the risk for HCC after HBsAg loss. They demonstrated that the overall pooled proportion of patients who have HCC after HBsAg loss is 2.29% (95% CI: 1.19%-4.37%). When only patients without cirrhosis and coinfection with hepatitis C virus were included, the pooled proportion of HCC development was 1.55% (95% CI: 0.92%-2.61%).

Kuang et al.[21] performed a systematic review and meta-analyses evaluating the risk factors for HCC development after HBsAg loss. The presence of cirrhosis, male sex, and age >50 years at the time of HBsAg loss were significant risk factors for HCC development, and HCC surveillance should be continued in individuals with any of these risk factors. This may be related to a higher fibrosis stage associated with later seroconversion in life, as seen in a cohort from New Zealand demonstrating that earlier HBsAg loss was associated with lower liver stiffness measurements.[22]

DURABILITY OF HBSAG SEROCONVERSION AND FACTORS THAT AFFECT SEROREVERSION

A recent study by Alawad et al.[23] followed 89 patients with HBsAg loss (both spontaneous and treatment related) for almost 10 years and showed that 95% remained HBsAg negative. Another study pooled data from three phase 3 clinical trials of patients treated with NUC monotherapy or pegylated interferon ± NUC therapy and found that HBsAg loss was durable in 82% with a median follow-up of 96 weeks.[24] In this study, anti-HBs seroconversion was not significantly associated with HBsAg seroreversion. Consolidation of treatment >12 weeks and confirmation of HBsAg >12 weeks after HBsAg loss were significantly associated with less seroreversion. From Korea, Kim et al.[25] showed that HBsAg loss was durable in 84% (92/110) of patients after a total follow-up of 287 patient-years after HBsAg loss.

CONCLUSION

HBsAg loss or functional cure has recently been adopted as a goal for antiviral therapy. However, it is a relatively uncommon event in patients with CHB, either spontaneously or under treatment, with a meta-analysis showing no difference between the two groups. Discontinuing NUCs is an emerging strategy to achieve HBsAg loss, but the data are rather heterogenous. A meta-analysis suggests that qHBsAg <100 IU/mL at the time of discontinuation leads to high rates of HBsAg loss. HBsAg loss is associated with significantly lower hepatic decompensation rates, less HCC, and better outcomes, especially when attained earlier than 50 years old and prior to the onset of cirrhosis. Consequently, HBsAg loss is a validated endpoint, but better antiviral therapies are needed to improve this.

CORRESPONDENCE

Seng Gee Lim, Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, 1E, Kent Ridge Road, NUHS Tower Block Level 10, Singapore 119228. E-mail: mdclimsg@nus.edu.sg

REFERENCES

1) World Health Organization, World Health Organization, Global Hepatitis Programme. Global hepatitis report, 2017. Available at: http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1. Accessed September 9, 2019.

2) Lok ASF, McMahon BJ, Brown RS, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. Hepatology 2016;63:284-306.

3) World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Available at: http://www.who.int/hepatitis/publications/hepatitis-b-guidelines/en/. Accessed September 20, 2019.

4) Cornberg M, Lok AS-F, Terrault NA, et al.; 2019 EASL-AASLD HBV Treatment Endpoints Conference Faculty. Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference. J Hepatol 2019;72:P539-P557.

5) Yeo YH, Ho HJ, Yang H-I, et al. Factors associated with rates of HBsAg seroclearance in adults with chronic HBV infection: a systematic review and meta-analysis. Gastroenterology 2019;156:635-646.e9.

6) Zhou K, Contag C, Whitaker E, et al. Spontaneous loss of surface antigen among adults living with chronic hepatitis B virus infection: a systematic review and pooled meta-analyses. Lancet Gastroenterol Hepatol 2019;4:227-238.

7) Hadziyannis SJ, Sevastianos V, Rapti I, et al. Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop long-term treatment with adefovir. Gastroenterology 2012;143:629-636.e1.

8) Hung C-H, Wang J-H, Lu S-N, et al. Hepatitis B surface antigen loss and clinical outcomes between HBeAg-negative cirrhosis patients who discontinued or continued nucleoside analogue therapy. J Viral Hepat 2017;24:599-607.

9) Liem KS, Fung S, Wong DK, et al. Limited sustained response after stopping nucleos(t)ide analogues in patients with chronic hepatitis B: results from a randomised controlled trial (Toronto STOP study). Gut 2019;68:2206-2213.

10) Seto W-K, Hui AJ, Wong VW-S, et al. Treatment cessation of entecavir in Asian patients with hepatitis B e antigen negative chronic hepatitis B: a multicentre prospective study. Gut 2015;64:667-672.

11) Liu J, Li T, Zhang L, et al. The role of hepatitis B surface antigen in nucleos(t)ide analogues cessation among Asian patients with chronic hepatitis B: a systematic review. Hepatology 2019;70:1045-1055.

12) Papatheodoridis G, Vlachogiannakos I, Cholongitas E, et al. Discontinuation of oral antivirals in chronic hepatitis B: a systematic review. Hepatology 2016;63:1481-1492.

13) Choi SJ, Anderson R, Lenz O, et al. LBP-02-Association between HBsAg loss and long-term clinical outcome in chronic hepatitis B: a systematic review and meta-analysis analysis. J Hepatol 2019;1:e141-e142.

14) Chen Y-C, Sheen I-S, Chu C-M, et al. Prognosis following spontaneous HBsAg seroclearance in chronic hepatitis B patients with or without concurrent infection. Gastroenterology 2002;123:1084-1089.

15) Arase Y, Ikeda K, Suzuki F, et al. Long-term outcome after hepatitis B surface antigen seroclearance in patients with chronic hepatitis B. Am J Med 2006;119:e9-e16.

16) Fattovich G, Giustina G, Sanchez-Tapias J, et al. Delayed clearance of serum HBsAg in compensated cirrhosis B: relation to interferon alpha therapy and disease prognosis. European Concerted Action on Viral Hepatitis (EUROHEP). Am J Gastroenterol 1998;93:896-900.

17) Chu C-M, Lin D-Y, Liaw Y-F. Clinical and virological characteristics post HBsAg seroclearance in hepatitis B virus carriers with hepatic steatosis versus those without. Dig Dis Sci 2013;1:275-281.

18) Chu C-M, Lin D-Y, Liaw Y-F. Does increased body mass index with hepatic steatosis contribute to seroclearance of hepatitis B virus (HBV) surface antigen in chronic HBV infection? Int J Obes (Lond) 2007;31:871-875.

19) Wang M-M, Wang G-S, Shen F, et al. Hepatic steatosis is highly prevalent in hepatitis B patients and negatively associated with virological factors. Dig Dis Sci 2014;59:2571-2579.

20) Liu F, Wang X-W, Chen L, et al. Systematic review with meta-analysis: development of hepatocellular carcinoma in chronic hepatitis B patients with hepatitis B surface antigen seroclearance. Aliment Pharmacol Ther 2016;43:1253-1261.

21) Kuang X-J, Jia R-R, Huo R-R, et al. Systematic review of risk factors of hepatocellular carcinoma after hepatitis B surface antigen seroclearance. J Viral Hepat 2018;25:1026-1037.

22) Lim TH, Gane E, Moyes C, et al. HBsAg loss in a New Zealand community study with 28-year follow-up: rates, predictors and long-term outcomes. Hepatol Int 2016;10:829-837.

23) Alawad AS, Auh S, Suarez D, et al. Durability of spontaneous and treatment-related loss of hepatitis B s antigen. Clin Gastroenterol Hepatol 2020;18:700-709.e3.

24) Lok AS, Zoulim F, Dusheiko G, et al. Durability of hepatitis B surface antigen loss with nucleotide analogue and peginterferon therapy in patients with chronic hepatitis B. Hepatol Commun 2020;4:8-20.

25) Kim G-A, Lim Y-S, 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.