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Original article

Management of Chronic Hepatitis B patients: HBsAg Kinetics

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Abstract

Hepatitis B is one of the most common infectious diseases in the world. Despite the high global burden of disease, and advances and available treatment options, most people infected with HBV and/or HCV remain unaware of their disease. Understanding HBsAg loss appears vital to achieving Hepatitis B virus infection cure drug development, optimization of disease detection, and patient management.

We aimed to define the HBs loss rate, describe HBs kinetics, identify factors associated with an HBs decline.

***Methods.** This retrospective cohort study was conducted using a database, that included 160 patients with chronic hepatitis B virus infection (treated and control groups). Enrolled patients had a long-term follow-up with several bloods analyzed over time.*

***Results.** Treated patients were older, had higher ALT and AST levels, higher HBV DNA. Serum HBsAg levels were 3,2 ± 0,9 and 3,0 ± 0,9 log IU/ml, HBV DNA levels were 2,6 ± 1,4 and 3,3 ± 1,8 log IU/ml, in treated and untreated patients, respectively. Inactive HBV carriers treated with pegylated interferon and nucleos(t)ide analogues accelerate the HBsAg decline and rate of HBsAg loss compared to untreated patients.*

***Conclusion.** The kinetics of serum HBsAg decline is more essential in treated patients when compared with untreated ones. This analysis confirms that a better understanding of HBsAg loss is essential for the development of effective drugs for the treatment of chronic hepatitis B and recommendations for optimizing early diagnosis to reduce the disease burden.*

***Keywords**: hepatitis B virus chronic infection, HBsAg loss, HBsAg kinetics, antiviral treatment.*

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Introduction

Hepatitis B virus infection (HBV) remains one of the most common chronic viral infections all over the world [1-3]. The World Health Organization (WHO) evaluated that more than 2 billion people worldwide have had contact with HBV [3]. About 290 million people are chronic carriers of HBV infection [4]. It results in around 1 million deaths worldwide every year from complications such as cirrhosis, hepatic decompensation, liver failure, and hepatocellular carcinoma (HCC) [2,4-5].

The HBsAg prevalence of HBV chronic infection varies geographically, from high (>8%, Asia, China, Africa, the Amazon Basin), intermediate (2-7%, Europe, the Middle East, Japan, South America) to low (<2%, North America, Northern, and Western Europe, Australia and New Zealand) prevalence [2,6-7]. Furthermore, this prevalence is differentiated by depending on socio-economic status, development of vaccination programs, and improvement of effective antiviral treatments as well as population movements and migration in the country [8].

The natural history of chronic HBV infection progresses through 5 phases [9-10]. Antiviral treatment's primary goal is to enhance the quality of life by preventing disease progression and early liver-related deaths. Each surrogate marker includes HBsAg or anti-HBs, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), HBV DNA, HBeAg or anti-HBe, and liver histology, are vital for monitoring the natural history and is known as a measure of the response to antiviral therapy.

HBsAg loss is an optimal endpoint as it indicates profound suppression of HBV replication and viral protein expression [1], enabling to safe discontinuation of antiviral therapy.

The development of standardized commercial assays has modernized interest in quantitative serum HBsAg as a biomarker to stratify the risk of disease progression, and relapse and predict treatment response. The measurement of HBsAg levels has been standardized in IU/ml, and currently it is one of the essential mandatory measurements due to the development of antiviral treatments aimed at HBsAg seroclearance, i.e., functional cure of CHB. HBsAg loss and seroclearance occur rarely in the natural history of CHB infection despite long-term antiviral treatment and is associated with a reduced risk of HCC [11-13].

HBsAg seroconversion is being associated with many factors as immune and viral. However, the immune mechanisms correlated with HBsAg seroclearance are still challenging to expound. In addition, HBs decline during current treatment is not well known [12].

HBsAg levels are essential in predicting HBsAg loss during follow-up. One Asian study found that in HBeAg-negative patients with persistently normal ALT, a decline ≥1 log10 IU/ml during 2-years or a single measurement below 200 IU/ml are the best predictors of HBsAg loss [positive predictive value (PPV) 100%] [14].

The on-treatment quantification of HBsAg can provide complementary information to HBV DNA levels to optimize the management of CHB [15].

A retrospective cohort study found a significant positive correlation between functionally cure time and baseline HBsAg [16]. A prospective study showed that lower baseline HBsAg level can predict CHB patients' response after their discontinuation of medication [17].

Also, a threshold of HBsAg decline ≥0,3 log10 IU/ml/year identifies patients with a high probability of HBsAg loss with a negative predictive value (NPV) of 95% and a PPV of 85% [18]. Later, the SEARCH□B cohort study enrolled 390 non□cirrhotic chronic hepatitis B (CHB) patients with spontaneous HBeAg seroconversion with an average follow□up of 7,4 years. Both lower HBV DNA and HBsAg levels were associated with a greater probability of HBsAg seroclearance. Areas under receiver operating characteristic (AUROC) curves for HBV DNA and HBsAg levels were compared to predict 6□year HBsAg seroclearance. HBsAg level was shown to be a better predictor than HBV DNA level (AUROC curve: 0.90 vs. 0.69, P=0.012). Even in patients with a very low viral load (HBV DNA level <200 IU/ml), the HBsAg level <100 IU/ml remained an independent predictor of HBsAg seroclearance [19-20].

The Food and Drug Administration guidance and most clinical studies outcome measures determine HBsAg seroclearance as a crucial indicator of thorough HBV clearance. A better understanding of HBsAg loss and decline, factors associated with HBs decline will contribute to develop of effective future therapies.

We conducted a retrospective study using the data of CHB patients. The primary objectives were to determine the HBs loss rate, describe HBs kinetics (HBs quantification decline), identify factors associated with an HBs decline >2 log UI/ml, then compare these results in this population, to an untreated cohort with HBV chronic infection.

We aimed to define the HBs loss rate, describe HBs kinetics, identify factors associated with an HBs decline.

Materials and methods

Patient cohort. A cohort of 160 patients, including 80 of treated and 80 of non-treated ones, with chronic HBV infection was selected for analysis according to HBs decline and HBs kinetics. We included only patients who have visited the Department of Hepatology at the Beaujon Hospital from 1991 to 2020 years, with HBsAg values available at least two times over one year, and met the following criteria: 1) no comorbid HCC or signs of hepatic decompensation; 2) no evidence of co-infection with hepatitis C virus, human immunodeficiency virus (HIV) and/or hepatitis delta virus; and (3) exclusion of other chronic liver disease causing agents (alcoholism, hepatotoxic drugs, and autoimmune liver disease); 4) adults, aged over 18 years. All participants had been HBsAg positive for more than 6 months before enrolling.

Data collection. We analyzed the medical records of each patient containing information about history, medical examination, liver disease activity and severity evaluation, and markers of HBV infection. The following medical information were collected: age, gender, ethnicity, serum AST and ALT levels, status of HBeAg serum (positive or negative), serum HBV-DNA and HBsAg titer, type of HBV genotype, liver elasticity indicator, type of treatment. These data were collected within all visits to the physician namely at baseline, during follow-up, and at the last visit. All enrolled participants underwent follow up more than 3 months with several blood analyzed over time. Treated patients have received NA, IFN-PEG or combination NA with IFN according to prescription of physician.

Laboratory measurements. Quantitative measurement of HBsAg was performed using automatized chemiluminescent microparticle immunoassay the Architect HBsAg QT (Abbott Diagnostics) assay, based on a calibration curve standardized by the WHO [21]. It measures HBsAg concentration from 0,05 to 250,00 IU/mL with a sensitivity of 99,8% and a specificity of 95% in two steps. Also, the other HBsAg quantification assay was an automated Roche Diagnostics Elecsys® HBsAg II screening assay which quantifies HBsAg concentration from 0,05 to 52000 UI/mL with a high specificity (>99,8%) [22]. Titers were expressed as log10 IU/ml. Besides HBeAg was measured using these immunoassays.

Cobas Taqman assay (Roche Diagnostics, Branchburg, NJ) with a linear range of 20–1.98×108 IU/mL measures serum HBV DNA levels. The Cobas TaqMan assay is a commercially available real-time PCR assay based on the co-amplification of target HBV DNA. Titers were expressed as log10 IU/ml. HBV genotype was defined in all patients using the INNO□LiPA HBV genotyping assay, which was performed according to the manufacturer's instructions (Innogenetics, Gent, Belgium).

Liver function parameters, including serum ALT, aspartate aminotransferase (AST) were measured using an automated biochemical analyzer. The UNL for ALT and AST serum was set at 40 U/L. We collected ALT and AST data every 3–6 months from medical records. FibroScan is used to evaluate the degree of liver scarring present (ie. stage of liver disease). The results are expressed in kilopascals (kPa). FibroScan® results range from 2.5 kPa to 75 kPa.

Statistical analysis. Data handling and analysis were performed using Microsoft Office Excel. Serum HBV DNA levels and HBsAg concentrations were logarithmically converted. Continuous variables were defined as mean ± standard deviation (SD) or median (range), and categorical variables as absolute and relative frequencies. The distribution normality was tested using the Kolmogorov-Smirnov test. Chi-square or Fisher's exact tests for categorical variables and Student's T-test or Mann-Whitney U test for continuous independent variables were conducted, as appropriate. Statistically significant results were considered values below p≤0,05.

Results

Patient Characteristics. One hundred and six patients (116 males, 44 female) meeting the inclusion criteria were included in the study. At inclusion 80 patients underwent various types of antiviral therapy. The 80 untreated patients constituted the control group (Table 1).

Table 1 - Baseline characteristics of CHB patients

	Untreated Patients	Treated Patients	
		NAs	NAs+IFN
Number (n)	80	65	15
Gender			
Male (n, %)	56, 70%	55, 77%	8, 67%
Female F (n, %)	24, 30%	15, 23%	4, 33%
Age (years) (mean ± SD)	38,6±10,1	44,8±12,4	45,5±9,9
Serum levels at inclusion			
AST (UI/L) (mediane)	25	30	43
ALT (UI/L) (mediane)	29	36	51
HBe-Ag negative (n, %)	78, 98%	60, 92%	11, 91%
HBV DNA (log10 IU/mL) (mean ± SD)	2,6±1,4	3,0±0,9	3,9±1,7
HBsAg quantification (mean ± SD, log10 UI/mL)	3,2±0,9	3,9±1,7	3,1±0,8

Treated patients were older, had higher serum ALT and AST levels, higher HBV DNA. Most patients were HBeAg-negative (n=122, 76%). Median age was 42 years. The median value of AST was 27 IU/ml. The median value of ALT was 33,5 IU/ml. Serum HBsAg levels were 3,2 ± 0,9 and 3,0 ± 0,9 log IU/ml, HBV DNA levels were 2,6 ± 1,4 and 3,3 ± 1,8 log IU/ml, in treated and untreated patients, respectively.

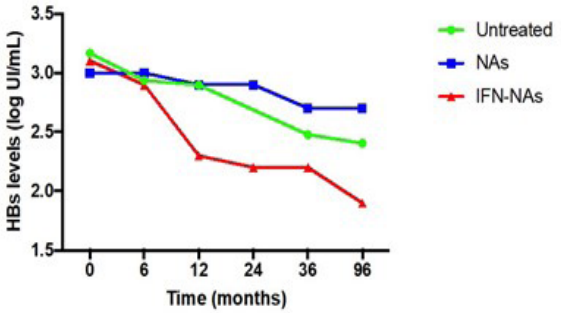

Figure 1 - HbsAg kinetics accordance to duration (months)

Treated patients. Baseline serum HBsAg and HBV DNA levels were 3,0 ± 0,9 and 3,3 ± 1,8 (p=0.114). At the end of therapy 51 patients were serum HBV DNA undetectable, 42 received NAs therapy, 2 received IFN and 7 – combination of drugs. At the end of follow-up serum HBsAg levels were 1,982±1,527, 2,001±1,720 and 2,112±1,3 log IU/ml in patients treated with NAs, IFN and add-on therapy, respectively (p=0.169). None of the patients had side effects.

End of follow-up. Treated and untreated patients were followed for: 10±1 years and 11±1 years, respectively (p=0.076). Serum HBV DNA was undetectable the end of follow-up in 83 patients, 51 (61%) and 32 (39%) treated and untreated patients, respectively. An HBsAg decline was observed in 55 patients (68%) and 50 (62%) in treated and untreated patients, respectively (Figure 1-2). Among patients who demonstrated an HBsAg decline a HBsAg seroclearance was observed in 10 (18%) and 21 (42%) treated and untreated patients respectively.

End of follow-up in patients receiving therapy. An HBsAg decline was observed in 45 (81%), 8 (15%) and 2 (4%) of patients receiving NAs monotherapy, Peg IFN and combination

of therapies, respectively. HBsAg loss was observed at the end of therapy in 10 patients. At baseline, initiation of NUCs, Peg IFN and combination of therapies and end of therapy serum HBsAg levels were significantly lower in patients demonstrating an HBsAg loss than in patients HBsAg positive at the end of follow-up.

End of follow-up in patients no receiving therapy. An HBsAg decline was observed in 50 (62%) patients. HBsAg loss was observed at the end of therapy in 21 patients. At baseline serum HBsAg levels were significantly lower in patients demonstrating an HBsAg loss than in patients HBsAg positive at the end of follow-up (Figure 2).

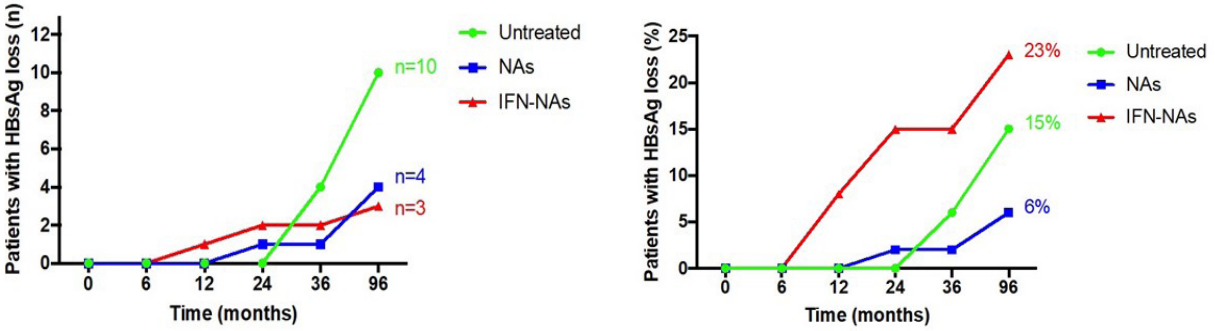

Figure 2 - HbsAg seroclearance according to duration (months)

Discussion

The priority goals of testing are to identify individuals with undiagnosed disease, as well as those most in need of treatment or at highest risk of transmission. People living with chronic hepatitis B should not be burdened with waiting for testing and treatment until complications occur. Diagnosis of hepatitis should be easily accessible so that people can aware about their diagnosis in a timely manner and receive life-saving treatment.

HBsAg loss and seroconversion to anti-HBs is considered to be the primary treatment objective, indicating a complete response to therapy and the outcome of the disease. It reflects immunological control of the infection and confers an excellent prognosis in the absence of preexisting cirrhosis or concurrent infections with other viruses [21].

We have investigated HBsAg kinetics under treatment and no-treatment in patients with CHB. Results indicated that an HBsAg decline was observed in 68% and 62% in treated and untreated patients, respectively. Among patients who demonstrated an HBsAg decline a HBsAg seroclearance was observed in 18% and 42% treated and untreated patients respectively.

P. Marcellin et al. [22] estimated that a significantly higher percentage of individuals who under NA plus PEG-IFN treatment for 48 weeks had a loss of HBsAg than those receiving NA or PEG-IFN alone. In our study, an HBsAg decline was observed more in patients receiving NAs monotherapy, then Peg-IFN and combination of therapies, respectively.

Alawad AS et al. [23] suggested that loss of HBsAg (either spontaneous or after treatment) was confirmed in 8% of HBsAg-positive patients. Seroconversion to anti-HBs increased over time and appeared to be more frequent after Peg-IFN treatment.

Study conducted by Mak LY et al. [24] demonstrated that among untreated patients HBsAg decreased steadily through the disease course and remains stable for a long time after HBeAg seroconversion. The number of HBsAg also reduced moderately in treated patients receiving NA.

In our study most patients were HBeAg-negative. In contrast, results of study carried out by Pfefferkorn et al. [25] estimated HBsAg predicts HBsAg loss during antiviral therapy of HBeAg-positive CHB patients. Findings of three-year follow up study of CHB patients treated with TDF [26] showed a greater decline in HBsAg titer at week 24 of therapy.

Our patients have genotype B or C infection. Previous studies showed that genotype is not considered as a major determinant of HBsAg kinetics [27-28].

This study has strengths: a well phenotype cohort with a long-term follow-up; an evaluation with several points with HBs quantification.

There are study limitations: it is not a randomized controlled trial; small sample size, which may bound the generalizability of the results; the lack of HBV genotype data.

Further research which using statistical analysis to define a suitable sample size for sufficient statistical power is warranted to validate the current findings.

Furthermore, close monitoring of quantitative HBsAg levels during treatment, in addition to the therapeutic value of baseline, also assistances predict response to therapy.

To sum up, to optimize the effect of successful treatment and prevention, interventions are needed to increase the use of testing services and improve linkage to care services, as well as to keep patients in the continuum of care, from initial screening to initiation of treatment and to achieve suppression of viral replication.

Conclusions

People with chronic hepatitis B should not be burdened with waiting for testing and treatment until complications occur. Diagnosis of hepatitis should be easily accessible so that people can learn about their diagnosis in a timely manner and receive life-saving treatment.

Treated patients were older, had higher serum ALT and AST levels, higher HBV DNA. At baseline serum HBsAg levels were significantly lower in patients demonstrating an HBsAg loss than in patients HBsAg positive at the end of follow-up. Patients treated had an HBsAg decline higher when compare to untreated patients. However, the mean HBsAg decline was minimal.

The changes in HBsAg kinetics defined by the results could provide a reference for future research investigating the use of serum HBsAg levels for response-guided management when sustained viral suppression is achieved with antiviral therapy.

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Abbreviations

ADV: Adefovir dipivoxil; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CHB: Chronic hepatitis B; cccDNA: covalently closed circular DNA; ETV: Entecavir; HBeAg: Hepatitis B e-antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HBV DNA: Hepatitis b viral load; HCC: Hepatocellular carcinoma; IFN: interferon; NAs: Nucleot(s)ide analogues; LAM: Lamivudine; PEG-IFN: pegylated interferon alpha; TBV: Telbivudine; TDF: Tenofovir; ULN: Upper limit of normal.

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Созылмалы В гепатиті бар науқастарды басқару: HBsAg кинетикасы

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Түйіндеме

В гепатиті әлемде кең тараған жұқпалы аурулардың бірі. Аурудың жоғары жаһандық ауыртпалығына, жетістіктерге және қол жетімді емдеу нұсқаларына қарамастан, ВГВ және/немесе ВГС жұқтырған адамдардың көпшілігі өз аурулары туралы білмейді. HBsAg антигенінің жоғалуын түсіну В гепатиті вирусының инфекциясын емдеуге, ауруды анықтауды оңтайландыруға және емделушілерді басқаруға арналған препараттарды әзірлеу үшін өте маңызды болып көрінеді.

Біздің мақсатымыз HBs жоғалту жылдамдығы анықтау, HBs кинетикасы сипатталды және HBs төмендеуіне байланысты факторлар анықтау болды.

Әдістері. Бұл ретроспективті когорттық зерттеу В гепатиті вирусынан туындаған созылмалы инфекциясы бар 160 пациентті (емдеу мен бақылау топтары) қамтитын мәліметтер базасын қолдана отырып жүргізілді. Тіркелген пациенттер уақыт өте келе бірнеше қан үлгілерін талдаумен ұзақ мерзімді бақылаудан өтті.

Нәтижесі. Емделген науқастар үлкенірек, АЛТ және АСТ деңгейі жоғары, В вирустық гепатиті ДНҚ жоғары болды. Қан сарысуындағы HBsAg деңгейлері тиісінше емделген және емделмеген пациенттерде 3,2 ± 0,9 және 3,0 ± 0,9 логарифмдік МЕ/мл, В вирустық гепатиті ДНҚ деңгейлері 2,6 ± 1,4 және 3,3 ± 1,8 логарифмдік МЕ/мл құрады. Пегилденген интерферон мен нуклеотид аналогтарын алған В вирустық гепатиті белсенді емес тасымалдаушылары емделмеген пациенттермен салыстырғанда HBsAg төмендеуі мен HBsAg жоғалту жылдамдығын тездетеді.

Қорытынды. Қан сарысуындағы HBsAg деңгейінің төмендеу кинетикасы емделмеген емделушілерге қарағанда емделген емделушілерде маңыздырақ. Бұл талдау созылмалы В гепатитін емдеуге арналған тиімді препараттарды және аурудың ауыртпалығын азайту үшін ерте диагностиканы оңтайландыру бойынша ұсыныстарды әзірлеу үшін HBsAg жоғалуын жақсы түсіну маңызды екенін растайды.

Түйін сөздер: В гепатиті вирусынан туындаған созылмалы инфекция, HBsAg жоғалуы, HBsAg кинетикасы, вирусқа қарсы емдеу.

Ведение пациентов с хроническим гепатитом В: кинетика HBsAg

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Резюме

Гепатит В является одним из самых распространенных инфекционных заболеваний в мире. Несмотря на высокое глобальное бремя болезни, а также на достижения и доступные варианты лечения, большинство инфицированных вирусами ВГВ и/или ВГС, людей остаются в неведении о своем заболевании. Понимание потери антигена HBsAg представляется жизненно важным для разработки лекарств для лечения вирусной инфекции гепатита В, оптимизации выявления заболевания и менеджмента пациентов.

В связи с этим, мы ставиили перед собой следующие цели: определение скорости потери HBs, описание кинетика HBs и выявление факторов, связанных со снижением HBs.

Методы. Данное ретроспективное когортное исследование было проведено с использованием базы данных, включавшей 160 пациентов с хронической инфекцией, вызванной вирусом гепатита В (группы лечения и контрольная

группа). Включенные в исследование пациенты проходили долгосрочное наблюдение с анализом нескольких образцов крови в течение определенного времени.

Результаты. Пролеченные пациенты были старше, имели более высокие уровни АЛТ и АСТ, более высокую ДНК HBV. Уровни HBsAg в сыворотке крови составили 3,2 ± 0,9 и 3,0 ± 0,9 логарифмических МЕ/мл, уровни ДНК HBV составили 2,6 ± 1,4 и 3,3 ± 1,8 логарифмических МЕ/мл у пролеченных и нелеченых пациентов соответственно. У неактивных носителей ВГВ инфекции, получавших пегилированный интерферон и нуклеотидные аналоги, наблюдалось ускорение снижения и скорости потери HBsAg в сравнении с пациентами, не получавшими лечения.

Выводы. Кинетика снижения уровня HBsAg в сыворотке крови более существенна у пролеченных пациентов по сравнению с пациентами, не получавшими лечение. Данный анализ подтверждает, что лучшее понимание потери HBsAg имеет важное значение для разработки эффективных препаратов для лечения хронического гепатита В и предложений по оптимизации ранней диагностики для снижения бремени заболевания.

Ключевые слова: хроническая инфекция, вызванная вирусом гепатита В, потеря HBsAg, кинетика HBsAg, противовирусное лечение.