MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 4665-4674
DOI: 10.12659/MSM.916441

Received: 2019.03.23
Accepted: 2019.06.03
Published: 2019.06.23

Early Serum HBsAg Drop Is a Strong Predictor of HBeAg Seroconversion and HBsAg Loss to Pegylated Interferon Alfa-2a in Chronic Hepatitis B Patients with Prior Nucleos(t)ide Analogue Exposure

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: This work was supported by National Natural Science Foundation of China [No. 81601522], Natural Science Foundation of Anhui Province [No. 1908085QH325], Natural Science Foundation of Jiangsu Province [No. BK20160348], Medical Youth Talent Project of Jiangsu Province [No. QNRC2016749], and the Science and Technology Project for the Youth of Suzhou [No. kjxw2015004]

Background: High rates of HBeAg and/or HBsAg seroconversion or clearance have been achieved in chronic hepatitis B (CHB) patients receiving pegylated interferon (pegIFN) in addition to ongoing nucleos(t)ide analogue (NUC) treatment. In the present study, we aimed to evaluate HBsAg kinetics to predict HBeAg seroconversion and HBsAg clearance in these patients.

Material/Methods: A total of 33 HBeAg-positive and 17 HBeAg-negative patients were enrolled between January 2010 and January 2018. At the end of pegIFN treatment, 9 of 50 patients achieved HBsAg clearance, and 9 of 33 HBeAg-positive patients achieved HBeAg seroconversion.

Results: The cutoff value of 0.41 $\log_{10}$ IU/mL in HBsAg decline at week 12 had a positive predictive value (PPV) of 58.3% and a negative predictive value (NPV) of 94.6% for HBsAg clearance. The cutoff value of 1.94 $\log_{10}$ IU/mL in HBsAg decline at week 24 had a PPV of 80.0% and an NPV of 97.5% for HBsAg clearance. The cutoff value of 0.47 $\log_{10}$ IU/mL in HBsAg decline at week 12 had a PPV of 83.3% and an NPV of 85.2% for HBeAg seroconversion. The cutoff value of 1.29 $\log_{10}$ IU/mL in in HBsAg decline at week 24 had a PPV of 85.7% and an NPV of 88.5% for HBeAg seroconversion.

Conclusions: Early HBsAg drop has a high predictive value for HBsAg clearance and HBeAg seroconversion in patients who were treated with combination therapy of pegIFN and NUCs.

MeSH Keywords: Hepatitis B • Hepatitis B e Antigens • Hepatitis B Surface Antigens

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/916441

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Background

Great progress has been achieved in treatment of chronic hepatitis B (CHB) in recent years [1,2]. Several nucleos(t)ide analogues (NUCs), including Entecavir, Telbivudine, and Tenofovir, are approved for suppressing HBV replication, and have been used to treat CHB for many years [3,4]. However, long-term treatment is necessary, and therapeutic effect remains indefinite [5,6]. Besides these direct antiviral agents, immune-modulating pegylated interferon (pegIFN) has been recommended [7,8]. pegIFN therapy has certain advantages: finite treatment duration, less development of resistance, high rate of HBeAg seroconversion, and HBsAg clearance or seroconversion in a few patients [9,10]. Nonetheless, pegIFN therapy disadvantages, including significant adverse effects and weak suppressive effect on HBV replication [11–13]. Therefore, combination therapies would be highly desirable. Researchers have reported achieving large reductions in HBsAg and high rates of HBeAg seroconversion through the combination of pegIFN and NUCs [13,14]. Because of HBsAg decline or HBeAg seroconversion based on sustained virologic response (SVR) [15], trials adding pegIFN to long-term NUC therapy in CHB patients show greater benefits [16,17]. However, this therapeutic strategy is not suitable for everyone. Actually, the optimal schedule of pegIFN therapy is affected by several factors, including low HBV DNA and HBsAg levels, high alanine aminotransferase (ALT), and high histologic activity index [18,19]. There is wide concern about how to identify and use indicators to predict treatment response to benefit selected patients.

Recent results have indicated that HBsAg and/or HBeAg are useful in predicting SVR, sustained HBeAg seroconversion, and/or HBsAg clearance to pegIFN alfa-2b [20–23]. However, little is known about the association between early HBsAg decline and HBeAg seroconversion/HBsAg clearance in pegIFN alfa-2a-treated patients with prior NUC exposure. In addition, protective HBsAb titer plays an important role in prevention of HBV infection [24]. However, it remains largely unexplored whether high-titer HBsAb is able to protect patients with HBsAg loss from rebound.

In this retrospective study, we predicted HBeAg seroconversion and HBsAg clearance by evaluating serum HBsAg kinetics in pegIFN alfa-2a-treated patients with prior NUC exposure. We also investigated the usefulness of hepatitis B vaccine in maintaining sustained HBsAg loss.

Material and Methods

Patients

A total of 50 patients with prior NUC exposure were selected in the present study, and these patients met the following criteria: adults (18–60 years old), positive HBsAg, positive or negative HBeAg, and completion of a 48-week course of add-on pegIFN alfa-2a treatment. Before pegIFN alfa-2a treatment, patients with cirrhosis, hepatocellular carcinoma (HCC), or NUC exposure less than 1 year were excluded. The study was approved by the Ethics Review Committee of the First Affiliated Hospital of Zhejiang University School of Medicine, and our experimental procedures were in agreement with the Declaration of Helsinki. Written informed consents were obtained from all participants for using their clinical records in this study.

Study design and definition

Patients with prior NUC exposure were subcutaneously administered additional pegIFN alfa-2a (Pegasys, Roche, Switzerland) at a dose of 180 μg or 135 μg once a week for 48 weeks. In consideration of previous NUC treatment effect, history of HBV *p* gene mutations, individual desires of patients and the economic conditions, the medication plan was adjusted as follows: ADV+pegIFN treatment (5 patients), ETV+pegIFN treatment (35 patients), and TDF+pegIFN treatment (10 patients). Based on the outcomes, patients were primarily designated as sustained virologic responders (SVR) and non-SVR. SVR was defined as undetectable HBV DNA both at the end of 48-week therapy and 6-month follow-up. Among patients with SVR, SVR-1 was defined as HBeAg seroconversion and HBsAg clearance at the end of a 48-week treatment of pegIFN alfa-2a; SVR-2 was defined as HBeAg seroconversion but no HBsAg clearance at the end of a 48-week treatment of pegIFN alfa-2a; and SVR-3 was defined as neither HBeAg seroconversion nor HBsAg clearance at the end of a 48-week treatment of pegIFN alfa-2a. During and after the 48-week combination therapy, patients who achieved HBsAg clearance received hepatitis B vaccine (Engerix B, GlaxoSmithKline Biologicals, Belgium) based on their individual desires and the economic conditions. The vaccine was given by intramuscular injection at a dose of 40 μg once every 2 weeks for 3 months to enhance HBsAb titer.

Laboratory measurements

HBV DNA was quantified by real-time PCR on a Roche LightCycler480 analyzer (Roche Diagnostics, Basel, Switzerland) with a limit of detection of 100 IU/mL. The levels of HBsAg, HBsAb, HBeAg, and HBeAb were determined by a chemiluminescent microparticle immunoassay using an Abbott I 2000 automated analyzer (Abbott Laboratories, Abbott Park, IL, USA).

Follow-up

Follow-up was conducted with all patients after pegIFN therapy. Clinical signs and symptoms of liver disease, as well as complications of liver diseases, were assessed. Laboratory measurements included ALT, aspartate aminotransferase (AST),

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Table 1. Baseline characteristics of NUC-experienced chronic hepatitis B patients.

	Overall		HBeAg-positive		HBeAg-negative	
Total number	50		33		17	
Age, years-median (range)	35	(20–53)	34	(20–53)	36	(21–51)
Gender (Male/Female)	38/12		26/7		12/5	
Ethnicity, N (%)						
Asian	50	(100%)	33	(100%)	17	(100%)
ALT normalization, N (%)	35	(70.0%)	22	(66.7%)	8	(47.1%)
ALT-median (range, U/L)	29	(9–525)	30	(9–425)	40	(9–525)
HBV DNA undetectability ,N (%)	27	(54.0%)	9	(27.3%)	1	(5.9%)
HBV DNA-median (range, log_{10} IU/mL)	4.3	(BLD–7)	4.2	(BLD–5.89)	4.4	(BLD–7)
HBsAg-median (range, IU/mL)	581	(3–15671)	906	(3–15671)	369	(65–4124)
HBeAg-median (range, PEIU/mL)	0.68	(0.01–351)	6.51	(1.0–351)	0.33	(0.01–0.98)
Duration of NUC treatment, years-median (range)	3	(1–10)	5	(2–10)	2.5	(1–9)
NUC-experienced monotherapy, N (%)	35	(70.0%)	21	(63.6%)	14	(82.4%)
Lamivudine	3		1		7	
Adefovir	10		7		5	
Entecavir	17		11		1	
Telbivudine	1		1		0	
Tenofovir	4		1		1	
NUC-experienced bitherapy, N (%)	15	(30.0%)	12	(36.4%)	3	(17.6%)
Adefovir+Entecavir	3		1		0	
Adefovir+Lamivudine	9		7		1	
Adefovir+Telbivudine	2		1		1	
Lamivudine+Entecavir	1		3		1	
HBV *P* gene mutations, N (%)	8	(16.0%)	2	(6.1%)	6	(35.3%)
rtL180M	3		1		2	
rtM204I	2		1		1	
rtL180M/M204I	1		0		1	
rtL180M/M204V	2		0		2	
HBV genotype (% B, C)	34.0, 66.0		36.4, 63.6		29.4, 70.6	

NUC – nucleos(T)ide analogue. HBV *P* gene, hepatitis B virus polymerase gene. BLD – below limited detection.

bilirubin, albumin/globulin, alpha-fetoprotein (AFP), HBV DNA, HBsAg, and HBeAg.

Statistical analysis

Data were statistically analyzed using SPSS statistical software package version 17.0 (SPSS, Chicago, USA). Continuous variables were expressed as mean ±SD or median (range). The χ^2-test, Mann-Whitney U-test, and Student's t-test were performed, as appropriate. The accuracy of HBsAg drop for prediction was assessed using the receiver operating characteristic (ROC) curve. The association between HBsAg decline and baseline factors was assessed by using univariate analysis and binary logistic regression analysis. All tests were 2-tailed, and $P<0.05$ was considered as statistically significant.

Results

Characteristics of patients

This was a retrospective study consisting of 50 consecutive patients. All patients with prior NUC exposure received additional pegIFN alfa-2a therapy in a 48-week treatment phase. Table 1 lists the baseline characteristics of patients before pegIFN alfa-2a therapy. There were 33 HBeAg-positive and 17

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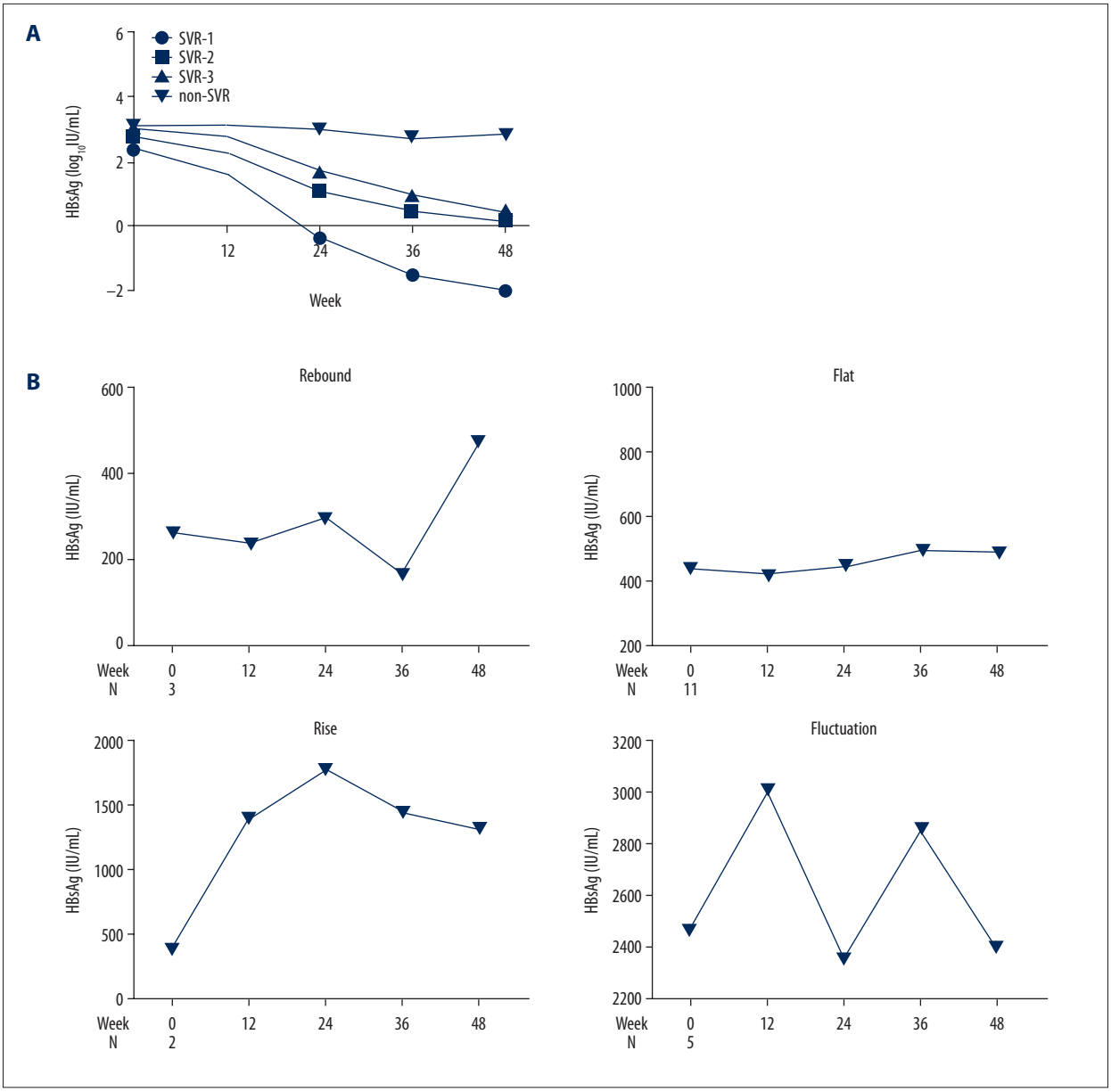

Figure 1. The kinetics of HBsAg levels in SVR-1, SVR-2, SVR-3, and non-SVR patients. (**A**) HBsAg levels (log_{10} IU/mL) in SVR-1, SVR-2, SVR-3, and non-SVR patients. (**B**) Kinetics of HBsAg levels in non-SVR patients. N – the number of patients.

HBeAg-negative patients. Patients were treated with monotherapy or combination therapy due to poor virologic response or drug resistance.

Clinical efficacy of a 48-week add-on pegIFN alfa-2a treatment in CHB patients

Of the enrolled patients, 18% (9/50) patients were SVR-1, 24% (12/50) patients were SVR-2, 16% (8/50) patients were SVR-3, and 42% (21/50) patients were non-SVR at the end of the 48-week treatment. In the HBeAg-positive group, SVR-1 occurred in 4 patients, exhibiting an incidence rate of 12.1% (4/33). SVR-2 patients accounted for 15.2% (5/33). Additionally, the incidence rates of SVR-3 and non-SVR were 24.2% (8/33) and 48.5% (16/33), respectively. In the HBeAg-negative group, SVR-1 occurred in 5 patients, exhibiting an incidence rate of 29.4% (5/17). SVR-2 patients accounted for 41.2% (7/17). Moreover, the incidence rates of SVR-3 and non-SVR were 0.0% (0/17) and 29.4% (5/17), respectively. The incidence rate of SVR-2 in the HBeAg-negative group was higher compared with the HBeAg-positive group (χ^2=4.166, P=0.041).

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Table 2. The association between HBsAg decline and baseline factors through univariate analysis.

	Declining group	Non-declining group	χ^2/t-test	*P* value
Total number	29	21		
Age, years-median (range)	36 (21–51)	34 (20–53)	0.275	0.784
Gender (Male/Female)	21/8	17/4	0.131	0.717
HBsAg-median (range, IU/mL)	378.2 (4.1–6785)	1119.2 (2.7–15671)	–1.529	0.133
Duration of NUC treatment, years-median (range)	5 (2–10)	2 (1–5)	5.633	<0.0001
HBV genotype-n (%)			2.993	0.084
B	14 (47.6)	5 (23.8)		
C	15 (52.4)	16 (76.2)		

Table 3. The association between HBsAg decline and baseline factors through binary logistic regression analysis.

	OR (95% CI)	*P* value
Age	1.10 (0.97–1.23)	0.129
HBsAg	1.00 (1.00–1.00)	0.487
Duration of NUCs treatment	0.24 (0.10–0.58)	0.002
HBV genotype, n (%)		0.334
B	1.00	
C	2.57 (0.38–17.40)	

HBsAg level is gradually decreased in SVR-1, SVR-2, and SVR-3 patients, but not in non-SVR patients

Figure 1A shows the median HBsAg level over time in SVR-1, SVR-2, SVR-3, and non-SVR patients. The HBsAg level in SVR-1, SVR-2, and SVR-3 patients was consistently decreased during the treatment. In contrast, the HBsAg level in non-SVR patients showed a slight reduction. Statistics showed that the HBsAg drop of SVR-1 was greater than that of non-SVR at week 12 (*P*=0.028), week 24 (*P*=0.007), week 36 (*P*=0.047), and week 48 (*P*=0.016). Moreover, the HBsAg drop of SVR-2 was greater than that of non-SVR at week 12 (*P*=0.036) and week 24 (*P*=0.009). In addition, the HBsAg drop of SVR-3 was greater than that of non-SVR at week 24 (*P*=0.011). Figure 1B illustrates the kinetics of HBsAg in non-SVR individuals who had several patterns of HBsAg dynamic changes, including rebound (3 patients), flat (11 patients), rise (2 patients), and fluctuation (5 patients). Tables 2 and 3 exhibit the association between HBsAg decline and baseline factors, such as age, gender, baseline HBsAg levels, duration of NUC treatment, and HBV genotype. The result indicated that the duration of NUC treatment was an independent factor for gradual HBsAg decline during the 48-week pegIFN alfa-2a treatment.

Predictive values of serum HBsAg kinetics on HBsAg clearance

Figure 2 shows that at week 12 of pegIFN alfa-2a treatment, 13 patients showed a decline of HBsAg level ≥0.41 $\log_{10}$ IU/mL. Among these patients, 53.8% achieved HBsAg clearance at the end of the 48-week therapy. Moreover, 37 patients showed a decline of HBsAg level <0.41 $\log_{10}$ IU/mL. Among these patients, 5.4% achieved HBsAg clearance at the end of the 48-week therapy. A chi-square test showed that the proportion difference was significant (χ^2=13.584, *P*=0.000228). At week 24 of treatment, 10 patients showed a decline in HBsAg level ≥1.94 $\log_{10}$ IU/mL. Among these patients, 80.0% achieved HBsAg clearance at the end of the 48-week therapy. In addition, 40 patients showed a decline of HBsAg level <1.94 $\log_{10}$ IU/mL. Among these patients, 2.5% achieved HBsAg clearance at the end of the 48-week therapy. Statistics revealed that there was a significant difference (χ^2=27.515, *P*=1.5586E-7).

At week 12, the cutoff value of 0.41 $\log_{10}$ IU/mL in HBsAg decline had a positive predictive value (PPV) of 58.3%, with a 95% confidence interval (CI) of 28.6-83.5%, and a negative predictive value (NPV) of 94.6% (95% CI, 80.5–99.1%). At week 24, the cutoff value of 1.94 $\log_{10}$ IU/mL in HBsAg decline had a PPV of 80.0% (95% CI, 44.2–96.5%) and an NPV of 97.5% (95% CI, 85.3-99.7%). We then assessed the accuracy of the cutoff values of 0.41 and 1.94 $\log_{10}$ IU/mL in HBsAg decline at week 12 and 24 of add-on pegIFN alfa-2a therapy to predict HBsAg clearance using the ROC. The area under the curve (AUC) was 0.870 at week 12 and 0.965 at week 24.

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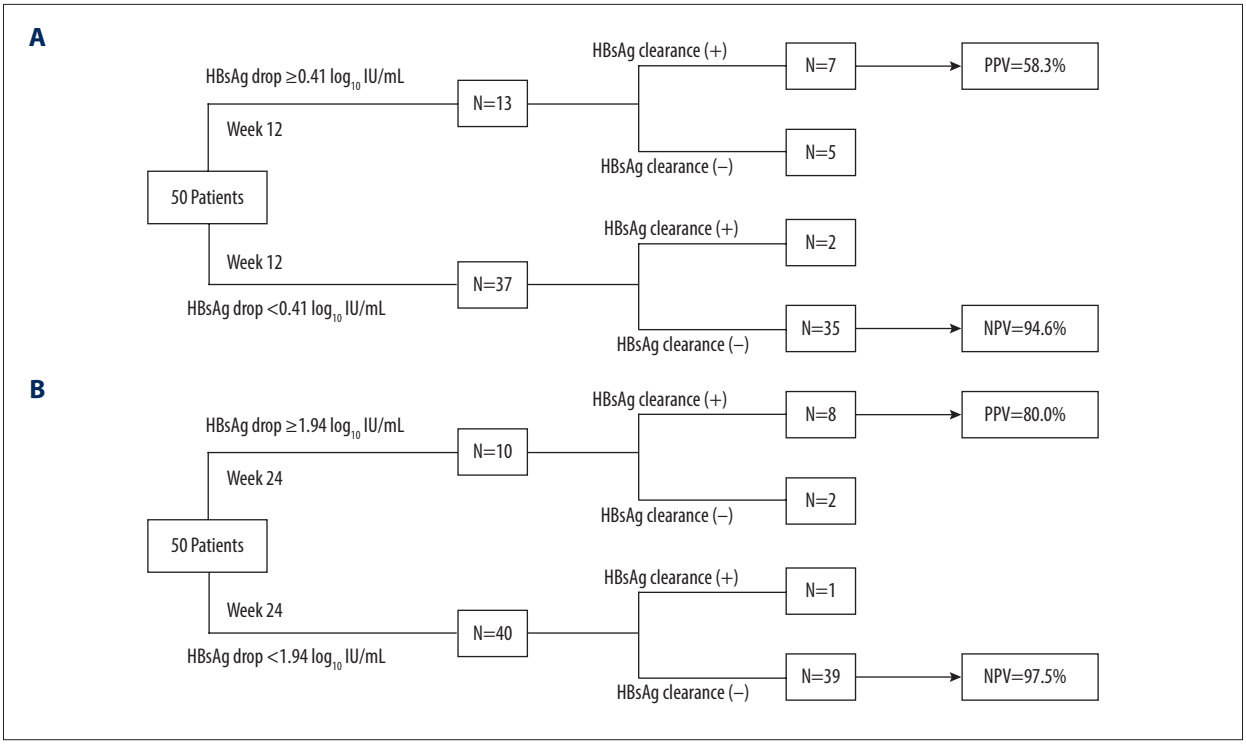

Figure 2. The predictive values of early HBsAg drop on HBsAg clearance. (**A**) Predictive values of the cutoff value of 0.41 $\log_{10}$ IU/mL in HBsAg decline at week 12. (**B**) Predictive values of the cutoff value of 1.94 $\log_{10}$ IU/mL in HBsAg decline at week 24. PPV, positive predictive value; NPV, negative predictive value.

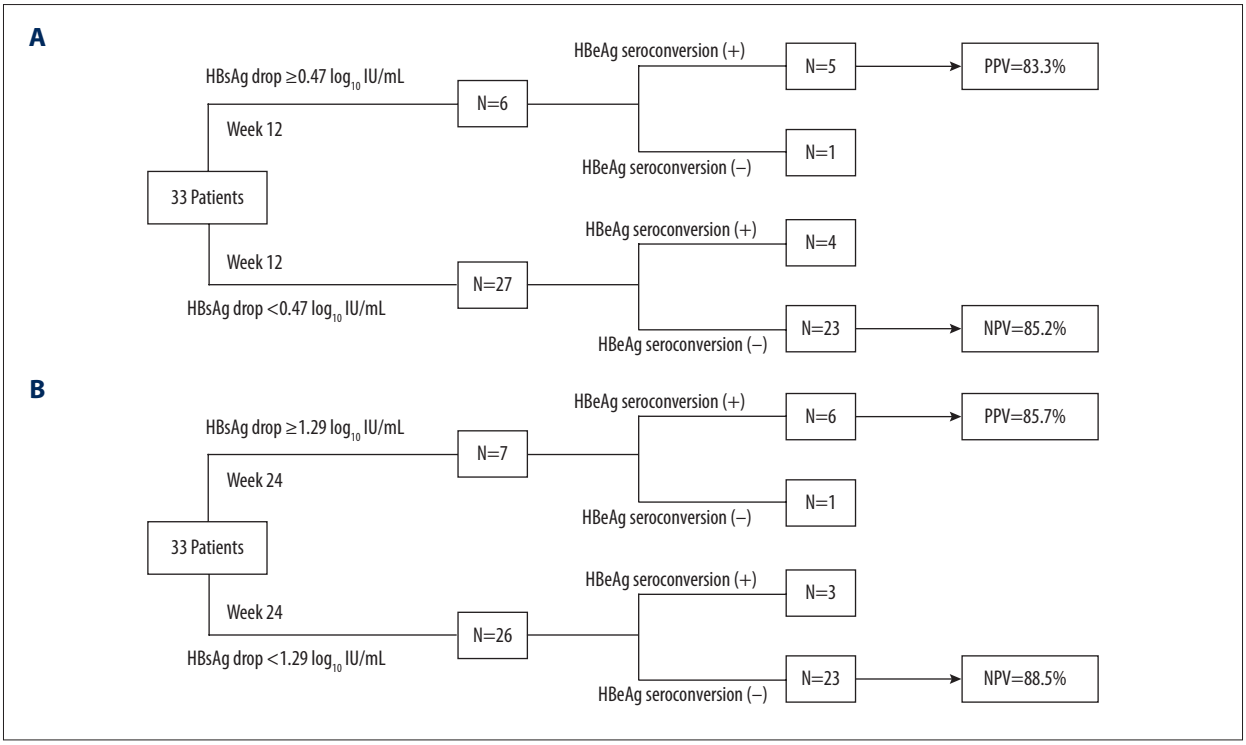

Figure 3. The predictive values of early HBsAg drop on HBeAg seroconversion. (**A**) Predictive values of the cutoff value of 0.47 $\log_{10}$ IU/mL in HBsAg decline at week 12. (**B**) Predictive values of the cutoff value of 1.29 $\log_{10}$ IU/mL in HBsAg decline at week 24.

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Predictive values of serum HBsAg kinetics on HBeAg seroconversion

Of 33 HBeAg-positive patients, 9 patients achieved HBeAg seroconversion at the end of 48 weeks. Figure 3 reveals that at week 12 of pegIFN alfa-2a treatment, 6 patients showed a decline of HBsAg level ≥0.47 $\log_{10}$ IU/mL. Among these patients, 83.3% achieved HBeAg seroconversion at the end of the 48-week therapy. Moreover, 27 patients showed a decline of HBsAg level <0.47 $\log_{10}$ IU/mL. Among these patients, 14.8% achieved HBeAg seroconversion at the end of the 48-week therapy. A chi-square test showed that the proportion difference was significant (χ^2=8.422, *P*=0.004). At week 24 of treatment, 7 patients showed a decline of HBsAg level ≥1.29 $\log_{10}$ IU/mL. Among these patients, 85.7% achieved HBeAg seroconversion at the end of the 48-week therapy. There were 26 patients who showed a decline in HBsAg level <1.29 $\log_{10}$ IU/mL. Among these patients, 11.5% achieved HBeAg seroconversion at the end of the 48-week therapy. Statistics indicated that there was a significant difference (χ^2=11.788, *P*=0.001).

At week 12, the cutoff value of 0.47 $\log_{10}$ IU/mL in HBsAg decline had a PPV of 83.3% (95% CI, 36.5–99.1%) and an NPV of 85.2% (95% CI, 65.4–95.1%). At week 24, the cutoff value of 1.29 $\log_{10}$ IU/mL in HBsAg decline had a PPV of 85.7% (95% CI, 42.0–99.2%) and an NPV of 88.5% (95% CI, 68.7–97.0%). We then assessed the accuracy of the cutoff values of 0.47 and 1.29 $\log_{10}$ IU/mL in HBsAg decline at week 12 and 24 of additional pegIFN alfa-2a therapy to predict HBeAg seroconversion using the ROC. The AUC was 0.787 at week 12 and 0.782 at week 24.

Serum kinetics of virologic markers during follow-up study

We suggested that patients with HBsAg clearance after completion of pegIFN treatment withdrawn from NUC treatment. However, patients without SVR, with or without HBeAg seroconversion, were suggested to receive continuous NUC treatment. Nine SVR-1 patients were followed up for about 1.0 year (range, 0.5–2.5 years) after additional pegIFN alfa-2a treatment. All of them maintained SVR and HBeAg seroconversion. Only 2 of them had slightly elevated HBsAg and became HBsAg-positive (from 0.02 IU/mL to 1.16 IU/mL, and from 0.02 IU/mL to 5.9 IU/mL, respectively). Moreover, 12 SVR-2 patients were followed up for about 2 years (range, 0.5–4 years). All of them maintained SVR, and, notably, 4 additional patients achieved HBsAg loss. Eight SVR-3 patients were followed up for about 2.5 years (range, 1.0–4 years). All of them maintained SVR, and HBeAg seroconversion occurred in 6 patients, while no patients achieved HBsAg loss. In addition, 21 non-SVR patients were followed up for about 2.5 years (range, 0.5–4 years), and undetectable HBV DNA (<100 IU/mL) was found in 15 patients. However, only 4 patients had HBeAg seroconversion, and no HBsAg loss occurred in these patients. Figure 4 shows the kinetics of median HBsAg and HBeAg concentrations in SVR-1, SVR-2, SVR-3, and non-SVR patients.

Discussion

It has been reported that HBsAg decline is more obvious in HBeAg-positive patients with continuous viral load reductions, as well as in HBeAg-negative patients with SVR [25,26]. Our study found that significant HBsAg decline was observed in SVR-1, SVR-2, and SVR-3 patients, but not in non-SVR patients. Further exploration revealed that the duration of NUC treatment, but not age, gender, baseline HBsAg levels, or HBV genotype, was an independent factor for gradual HBsAg decline during the 48-week treatment of add-on pegIFN alfa-2a. Actually, SVR-1, SVR-2 and SVR-3 patients had long-term NUC exposure before the pegIFN alfa-2a treatment, and the median duration of NUC treatment of these patients was about 5 years.

Based on the research on predictive value of HBsAg loss in CHB patients with long-term NUC treatment, Roeland has found that HBeAg-positive patients with SVR have a sharp HBsAg decline – the HBsAg decline is 1.91 $\log_{10}$ IU/mL in patients who will lose HBeAg, and the HBsAg decline of 1 $\log_{10}$ IU/mL from baseline is associated with HBsAg clearance [27]. Rami has reported that early HBsAg drop of 0.5 and 1 $\log_{10}$ IU/mL at weeks 12 and 24 of pegIFN therapy, respectively, has high predictive values of SVR [28]. Moreover, HBsAg and HBeAg levels are strong predictors of sustained HBeAg seroconversion in HBeAg-positive patients [22]. Our study focused on HBsAg decline as a predictor of HBeAg seroconversion and HBsAg clearance to add-on pegIFN alfa-2a therapy in NUC-experienced patients. Our results show that the cutoff value of 1.94 $\log_{10}$ IU/mL in HBsAg decline at week 24 had a higher predictive value of HBsAg clearance (AUC=0.965, PPV=80.0%, and NPV=97.5%). Furthermore, through investigating the association between early HBsAg drop and HBeAg seroconversion in 33 HBeAg-positive patients, we found that the HBsAg drop was also a strong predictor of HBeAg seroconversion at the end of the 48-week treatment. However, HBeAg drop did not predict HBsAg clearance in HBeAg-positive patients. In addition to the predictive values of HBsAg kinetics, we also quantitatively analyzed HBsAg and HBeAg at week 12 and week 24 to predict HBeAg seroconversion and HBsAg clearance. However, no predictive values were found.

It has been reported that hepatitis B vaccine is able to enhance HBsAb titer to achieve efficient protection in healthy individuals, which is not available to CHB patients [29,30]. However, it is unclear whether hepatitis B vaccine is useful for CHB patients who have achieved HBsAg clearance. In this study, of 13 patients who achieved HBsAg loss during and after pegIFN alfa-2a

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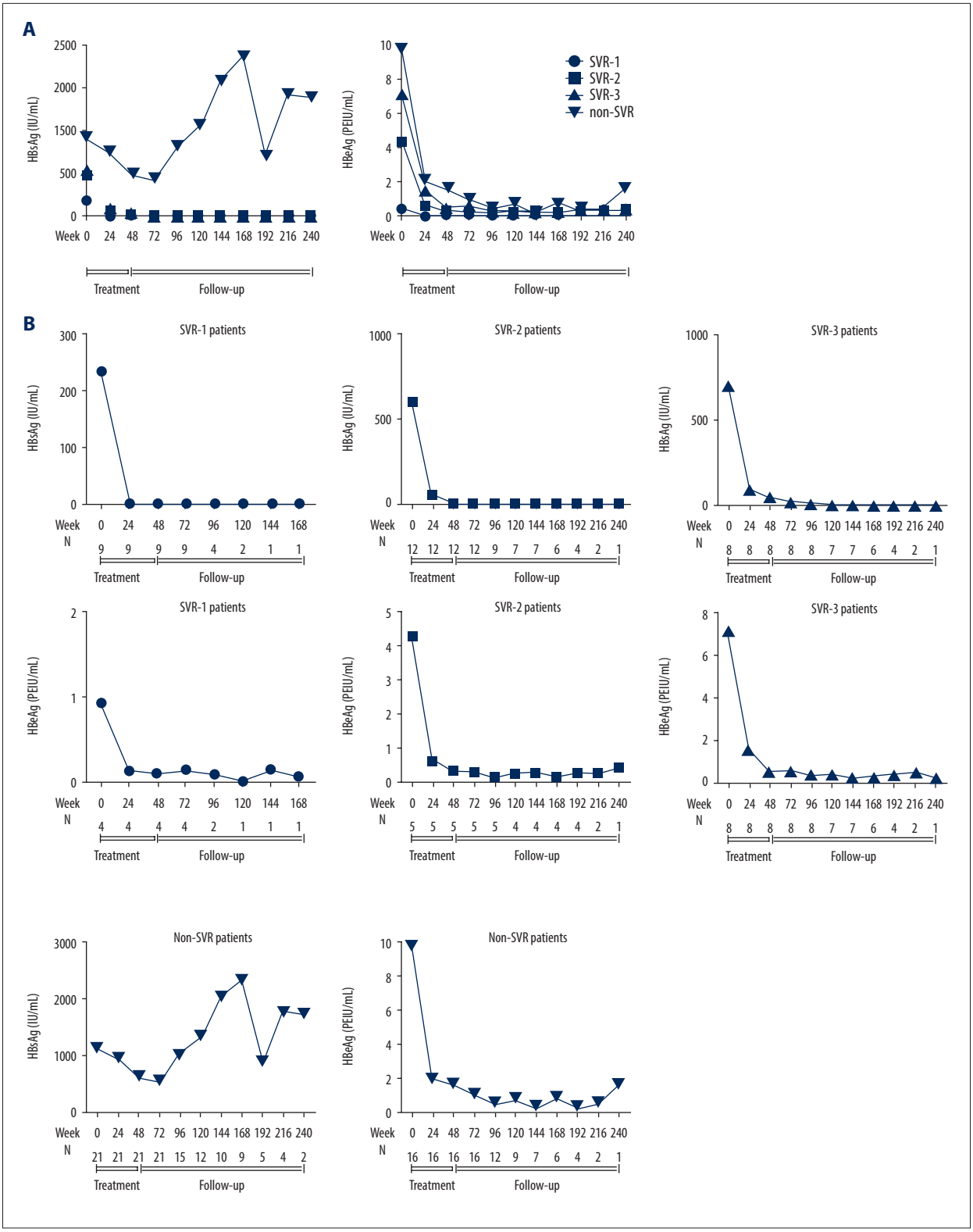

Figure 4. The kinetics of HBsAg and HBeAg levels in SVR-1, SVR-2, SVR-3, and non-SVR patients. (**A, B**) Kinetics of HBsAg and HBeAg levels in SVR-1, SVR-2, SVR-3, and non-SVR patients. N – numbers of treatment and follow-up of patients.

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treatment, 6 received hepatitis B vaccine, and the median HBsAb titer reached 664.5 mIU/mL (range, 68.3–1000.0 mIU/mL) after the 3-month course of vaccine injection. All of them remained high-titer HBsAb and maintained sustained HBsAg loss when the measurement was performed every 6 months. Seven patients did not receive hepatitis B vaccine when their HBsAg loss first appeared. Accompanying with the first appearance of HBsAg loss, the median HBsAb titer became positive but lower than 20.4 mIU/mL (range, 5.7–27.7 mIU/mL). From that moment, HBsAb titer was measured every 6 months, and it gradually declined. Notably, 2 of them became HBsAg-positive. Therefore, high-titer HBsAb induced by hepatitis B vaccine in patients who achieved HBsAg loss might be effective in maintaining sustained HBsAg loss. Besides, failure to achieve SVR, HBeAg seroconversion, or HBsAg clearance mostly resulted from HBV mutations or slight decrease in HBeAg and HBsAg during pegIFN treatment. Researchers have reported that, during a median 8.8-year follow-up, pegIFN-treated and HBeAg-seroconverted patients show decreased necroinflammatory activity, less progression of fibrosis, and low incidence of HCC [31]. Patients who receive pegIFN therapy have long-term benefits, including increased HBsAg seroclearance and reduced cirrhosis and/or HCC [32,33]. Our study also revealed that patients who achieved HBeAg seroconversion and/or HBsAg clearance had better prognosis. However, a previous investigation has shown that some individuals who are chronically infected with HBV eventually lose HBsAg, but HCC occurs in a few patients [34]. Therefore, longer follow-up is necessary. Although we found that HBeAg-negative patients displayed better outcomes during and after pegIFN alfa-2a treatment, we did not find a significant difference in the incidence rate of SVR-1 between HBeAg-positive and HBeAg-negative patients. We speculate that this could be attributed to the long-term NUC exposure of HBeAg-positive patients, some of who had low-level but positive HBeAg and HBsAg.

Collectively, early HBsAg changes showed high predictive values in the NUC-experienced patients who would obtain most benefits from add-on pegIFN alfa-2a treatment. Moreover, high-titer HBsAb induced by hepatitis B vaccine was helpful in maintaining sustained HBsAg clearance.

Conclusions

Our results indicated that early reduction of serum HBsAg is a useful tool to predict treatment response of patients. To the best of our knowledge, this is the first published study on the usefulness of hepatitis B vaccine in protecting patients with HBsAg loss from rebound.

Conflict of interest

None.

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