MAJOR ARTICLE

HBsAg Profiles in Patients Receiving Peginterferon Alfa-2a plus Ribavirin for the Treatment of Dual Chronic Infection with Hepatitis B and C Viruses

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Background. With use of peginterferon alfa-2a and ribavirin combination therapy in patients with dual chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, 11.2% of patients achieved clearance of hepatitis B surface antigen (HBsAg) at 6 months after treatment; however, reactivation of HBV DNA was observed in 36.3%. We investigated the predictive potential of HBsAg quantification.

Methods. HBsAg quantification was performed in 120 e antigen–negative patients dually infected with HBV and hepatitis C virus and treated with peginterferon alfa-2a/ribavirin for 48 weeks (HCV genotype 1; $n = 74$) or 24 weeks (HCV genotype 2/3; $n = 46$). HBsAg was quantified at baseline, week 4, week 12, end of treatment, and 24 weeks after treatment.

Results. The baseline median serum HBsAg level was 120 IU/mL and decreased gradually during treatment. Low baseline HBsAg was significantly associated with HBsAg clearance (40% for HBsAg level $\leq$20 IU/mL vs 2.2% for HBsAg level >20 IU/mL; $P < .05$). A decrease in HBsAg level from baseline to week 12 of 50% was associated with a reduced likelihood of HBV DNA reactivation in patients with baseline undetectable serum HBV DNA (positive predictive value, 89.5%).

Conclusions. HBsAg quantification appears to be a useful indicator of posttreatment outcome in patients dually infected with HBV and hepatitis C virus.

Hepatitis B virus (HBV) infection is a worldwide health problem [1]. Several oral nucleos(t)ide analogues potent in the suppression of HBV replication are currently approved for the treatment of patients with chronic hepatitis B (CHB) [2]. However, prolonged treatment is usually needed to maintain the suppression of viral replication, particularly in patients with hepatitis B e antigen (HBeAg)–negative CHB, because rebound occurs in $\geq$90% of patients if the drug is discontinued [3]. In parallel with analogues, peginterferon alfa-2a (PEG-IFN) has been advocated as a first-line therapy in patients with CHB [2, 4–6], because of its immunomodulatory as well as antiviral properties. The advantages of PEG-IFN therapy include a lack of drug resistance, a finite and defined treatment course, and a higher likelihood for hepatitis B surface antigen (HBsAg) clearance, compared with nucleos(t)ide analogues [4]. The latter is regarded as a complete or ideal response to therapy in patients with CHB [2, 5, 7].

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Despite these potential benefits, use of PEG-IFN therapy is low compared with nucleos(t)ide analogues in many countries [8], including Taiwan, which is likely related to the profile of its adverse effects, the inconvenience associated with subcutaneous injection, the relatively lower antiviral potency of PEG-IFN compared with analogues, and the fact that not all patients achieve a sustained response.

Predictors that allow the selection of patients who will likely benefit from a finite course of PEG-IFN or who have a low likelihood of response would be of great relevance for clinicians [9, 10]. The potential of HBsAg quantification during interferon-based therapy to predict sustained response in both HBeAg-positive and HBeAg-negative CHB has been suggested [11–15].

Dual chronic infection with hepatitis C virus (HCV) and HBV is common in areas endemic for either virus [16–19]. Interferon plus ribavirin combination therapy has been shown to be effective in the clearance of HCV in this population [20–23]. In our recent trial, we treated patients with HBeAg-negative CHB and concurrent active hepatitis C by using PEG-IFN plus ribavirin combination therapy. We found that posttreatment HBsAg clearance at 6 months of follow-up was achieved in 11.2% of patients [24]. On the other hand, we observed that inactive HBV infection may reactivate during the treatment of coexisting chronic hepatitis C; serum HBV DNA reappeared posttreatment in 36.3% of our patients in whom HBV DNA was undetectable at baseline. Given the substantial risk of hepatitis activity flare-up associated with HBV DNA reactivation [25, 26], it would be of great clinical relevance to identify as early as possible those inactive carriers who will remain inactive or are likely to experience hepatitis B reactivation and, thus, require additional antiviral therapy intervention. The aim of this study was to examine the profiles and predictive value of HBsAg level for HBsAg clearance and lack of HBV DNA reactivation in patients dually infected with HCV and HBV and undergoing therapy with PEG-IFN and ribavirin.

PATIENTS AND METHODS

Collection of patients. In our original trial, we enrolled 161 eligible Taiwanese patients with active hepatitis C (alanine aminotransferase [ALT] level >1.5 times upper limit of normal and serum HCV RNA >200 IU/mL) and concurrent HBeAg-negative CHB, as described elsewhere [20]. Patients with HBeAg-negative chronic HBV infection was further classified in 2 categories: those with detectable HBV DNA (>200 IU/mL or >1000 copies/mL) at baseline, who were considered to have active HBeAg-negative CHB, and those with undetectable HBV DNA (<200 IU/mL or <1000 copies/mL), who were considered to be inactive HBsAg carriers at baseline. Patients with HCV genotype 1 infection received 48 weeks of PEG-IFN 180 μg/week plus 1000–1200 mg ribavirin daily. Patients infected with genotype 2/3 received 24 weeks of PEG-IFN weekly plus 800 mg ribavirin daily.

On-treatment serum samples of all 120 dually infected patients (HCV genotype 1 coinfection, group I, $n = 74$; HCV genotype 2/3 coinfection, group II, $n = 46$) from the original trial cohort in 3 study sites (National Taiwan University Hospital, Kaohsiung Medical University Hospital, and Chang Gung Memorial Hospital-Kaohsiung) were collected. This study investigated the profiles of serum HBsAg level in the 120 patients for whom serum samples were available.

On-treatment monitoring of HBsAg. HBsAg was quantified at baseline, week 4, week 12, week 24, end of treatment (48 weeks in group I or 24 weeks in group II), and 24 weeks posttreatment (72 weeks in group I or 48 weeks in group II) with use of a standard quantitative chemiluminescent microparticle immunoassay (ARCHITECT HBsAg, Abbott Diagnostics). The concentration of HBsAg in the specimen was determined using a previously generated Architect HBsAg calibration curve (range, 0.05–250 IU/mL). Serum HBsAg <0.05 IU/mL was defined as clearance of HBsAg. Samples with serum HBsAg titer >250 IU/mL were diluted at 1:20 and 1:500 with the Architect HBsAg diluent and retested to expand the upper limit of the dynamic range from 250 to 125,000 IU/mL.

Quantification of serum HBV DNA. We used an in-house real-time polymerase chain reaction assay for quantification and genotyping of HBV DNA, as described elsewhere [27]. The detection limit of this assay for HBV DNA was 1000 copies/mL (or 200 IU/mL).

Ethical considerations. The study was conducted according to the 1975 Declaration of Helsinki and Good Clinical Practice as reflected in a priori approval by the institutional human research committee. All patients gave written informed consent.

Statistical analysis. All categorical and continuous variables were analyzed by χ^2 test and Student's t test, respectively. For continuous variables with outliers, nonparametric tests were used. The accuracy of a serum HBsAg decrease to predict responses and reactivation of serum HBV DNA was assessed using the receiver operating characteristic curve. All tests were 2-sided and used a significance level of 0.05. All analyses were performed by using Stata statistical software (Version 8.2; StataCorp).

RESULTS

Baseline characteristics. The baseline characteristics of the dually infected patients in the subgroup of 120 patients included in the current analysis are shown in Table 1.

HBV serologic response, virologic response, and reactivation. Overall, clearance of HBsAg was documented in 11 (9.2%) and 14 (11.7%) of the 120 dually infected patients at end of treatment and end of follow-up, respectively. In addition, serocon-

Table 1. Characteristics of the 120 Patients at Baseline

Characteristic	Patients (n = 120)
Male sex, no (%) of patients	78 (65)
Age, mean years ± SD	50.6 ± 9.6
Body weight, mean kg ± SD	68.4 ± 13.3
BMI, mean kg/m^2 ± SD	25.4 ± 3.6
HCV RNA, mean IU/mL ± SD	8.36×10^5 (478 to 1.01×10^8)
HBV DNA positivity,[a] no (%) of patients	58 (48)
HBV DNA,[a] mean copies/mL ± SD	1280 (undetectable to 4.22×10^5)
HBV genotype, no of patients with B/C/mixed/undetectable	46/17/4/53
ALT, mean IU/L ± SD	128 ± 84
Histologic stage of fibrosis, no of patients with 0/1/2/3/4	6/18/45/36/15
Stage of fibrosis, mean stage ± SD	2.25 ± 1.21

NOTE. ALT, alanine aminotransferase; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HBV, hepatitis B virus; HCV, hepatitis C virus; SD, standard deviation.

[a] Baseline serum HBV DNA level was determined by an in-house real-time polymerase chain reaction assay. Levels >1000 copies/mL (200 IU/mL) were defined as positive.

version to anti-HBs was observed in 7 (50%) of the 14 patients at end of follow-up.

Of the 120 dually infected patients with available serum samples, 58 (48.3%) had detectable serum HBV DNA at baseline (active HBeAg-negative chronic hepatitis B). The median value of serum HBV DNA levels in these patients was 12,800 copies/mL (range, 1050–1,020,000 copies/mL). HBV virologic response, defined by a reduction of serum HBV DNA to an undetectable level (<1000 copies/mL or <200 IU/mL) at 6 months after the end of therapy, was observed in 34 patients (58.6%). Of the remaining 62 patients with undetectable baseline serum HBV DNA (inactive HBsAg carriers), reactivation of serum HBV DNA, defined by an elevation of serum HBV DNA to >200 IU/mL (>1000 copies/mL) at the end of therapy or thereafter, was observed in 21 patients (33.9%) (n = 13 in group I and n = 8 in group II).

Serum HBsAg kinetics. The baseline median serum HBsAg level was 120 IU/mL (range, 0.8–11,556 IU/mL). Baseline HBsAg levels were divided into 4 quartiles: ⩽20 IU/mL (n = 30), 21–120 IU/mL (n = 31), 121–600 IU/mL (n = 29), and >600 IU/mL (n = 30). During treatment, serum HBsAg level decreased gradually. As shown in Table 2, the proportion of patients achieving serum HBsAg levels ⩽20 IU/mL increased from 27% (n = 20) at baseline to 50% (n = 37) at end of follow-up in group I (48 weeks treatment) and increased from 21.7% (n = 10) at baseline to 45.7% (n = 21) at end of follow-up in group II (24 weeks treatment). The proportion of patients with serum HBsAg levels >600 IU/mL decreased from 25.7% (n = 19) at

Table 2. Distribution of Serum Hepatitis B Antigen (HBsAg) Levels in Patients Receiving 48-Week or 24-Week Peginterferon Alfa-2a (PEG-IFN) plus Ribavirin (RBV) Combination Therapy

	Treatment group, no (%) of patients					
	48-week PEG-IFN plus RBV			24-week PEG-IFN plus RBV		
HBsAg level, IU/mL	Baseline (n = 74)	Week 48[a,b] (n = 73)	Week 72[c] (n = 74)	Baseline (n = 46)	Week 24[b] (n = 46)	Week 48[c] (n = 46)
⩽20	20 (27.0)	35 (48.0)	37 (50.0)	10 (21.7)	20 (43.5)	21 (45.7)
21–120	18 (24.3)	14 (19.2)	12 (16.2)	13 (28.3)	11 (23.9)	13 (28.3)
121–600	17 (23.0)	13 (17.8)	13 (17.6)	12 (26.1)	8 (17.4)	7 (15.2)
>600	19 (25.7)	11 (15.0)	12 (16.2)	11 (23.9)	7 (15.2)	5 (10.9)

[a] Data were missing for 1 patient.
[b] End of treatment.
[c] End of follow-up.

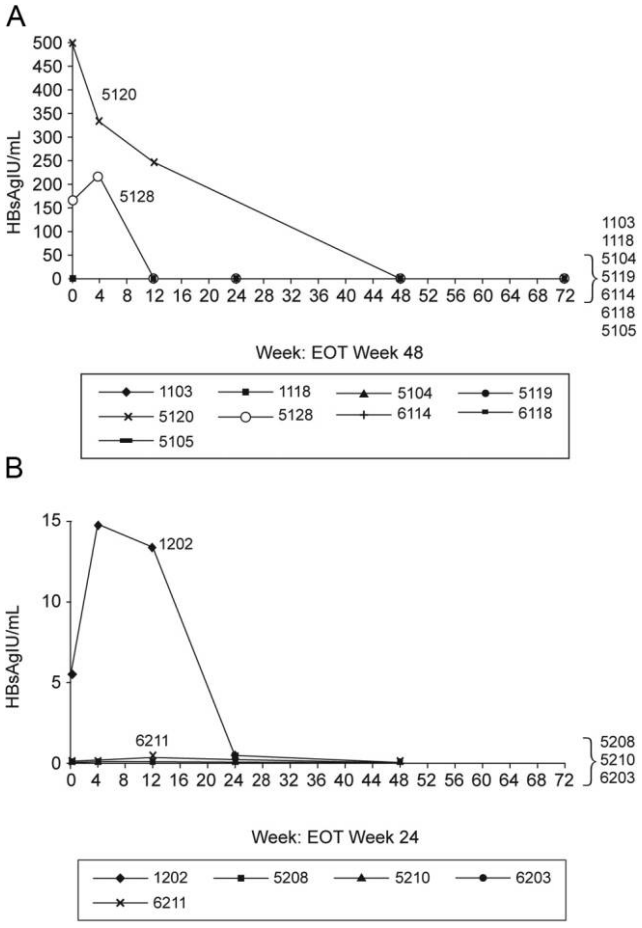

Figure 1. Profiles of hepatitis B surface antigen (HBsAg) in patients who cleared HBsAg posttreatment in 9 patients receiving 48-week peginterferon alfa-2a (PEG-IFN) plus ribavirin therapy (*A*) and in 5 patients receiving 24-week PEG-IFN plus ribavirin therapy (*B*). Serum HBsAg level remains low during the treatment period in 11 patients (Cases 1103, 1118, 5104, 5105, 5119, 6114, and 6118 in panel *A*; Cases 5208, 5210, and 6203 in panel *B*). EOT, end of treatment.

baseline to 16.2% ($n = 12$) at end of follow-up in group I and decreased from 23.9% ($n = 11$) at baseline to 10.9% ($n = 5$) at end of follow-up in group II.

Profiles of serum HBsAg in patients who cleared HBsAg. Clearance of HBsAg 6 months posttreatment occurred in a total of 14 patients, 9 group I patients and 5 group II patients. The median serum HBsAg level was 1.8 IU/mL at baseline. The serum HBsAg level at baseline in the 14 patients who cleared HBsAg was significantly lower than that in the 106 patients without HBsAg clearance ($P < .001$). Five of the 14 patients with HBsAg clearance had detectable serum HBV DNA at baseline, and all developed an HBV virologic response.

The profiles of serum HBsAg in the 14 patients who cleared HBsAg are further shown in Figure 1*A* (group I) and Figure 1*B* (group II). Baseline HBsAg levels in 11 (78.6%) of these 14 patients were quite low (<5 IU/mL). Serum HBsAg level remained low during the treatment period in these 11 patients (Cases 1103, 1118, 5104, 5105, 5119, 6114, and 6118 in Figure 1*A*; Cases 5208, 5210, and 6203 in Figure 1*B*). Two group I patients (Case 5120 and Case 5128) had relatively high baseline serum HBsAg levels (508 IU/mL and 163 IU/mL, respectively), compared with the overall median level (120 IU/mL), and showed a profound decrease of serum HBsAg during treatment. Figure 2 illustrates the kinetics of serum HBV DNA, HCV RNA, HBsAg, and ALT levels in these 2 individual patients. In the first patient (Case 5120), HBsAg and HBV DNA showed parallel decline kinetics, and clearance of HBsAg occurred at the end of therapy when HBV DNA became undetectable (Figure 2*A*). In the second patient (Case 5128), HBsAg kinetics showed a gradual decrease after the start of therapy. HBsAg clearance occurred 24 weeks after treatment cessation. Serum HBV DNA however remained undetectable throughout the treatment and follow-up period (Figure 2*B*). Notably, anti-HBs antibody was positive (>10 mIU/mL) in the first patient at 6 months posttreatment. HCV sustained virologic response was obtained in both of these cases.

The HBsAg clearance rate among the 30 patients with baseline serum HBsAg ⩽20 IU/mL (40%; $n = 12$) was significantly greater than that among the 90 patients with baseline serum HBsAg >20 IU/mL (2.2%; $n = 2$; $P < .05$). Accordingly, the cutoff of serum HBsAg level ⩽20 IU/mL at baseline had a sensitivity of 85.7%, a specificity of 84%, a positive predictive value (PPV) of 41.4%, a negative predictive value (NPV) of 97.8%, and a likelihood ratio of 5.36 for HBsAg clearance 6 months posttreatment. The accuracy of the cutoff of serum HBsAg level ⩽20 IU/mL at baseline to predict HBsAg clearance 6 months posttreatment was assessed using the receiver operating characteristic curve. The area under the curve (AUC) was 0.912 (95% confidence interval, 0.802–1.021; $P < .001$).

In addition to baseline serum HBsAg level, we also examined the predictive value of on-treatment HBsAg level for posttreatment HBsAg clearance. At week 4, the cutoff of 35% decrease in HBsAg level from baseline had a sensitivity of 53.8%, a specificity of 80.4%, a PPV of 26.9%, an NPV of 92.9%, and a likelihood ratio of 2.89 to predict HBsAg clearance 6 months posttreatment (AUC, 0.657). At week 12, the cutoff of 50% decrease in HBsAg level from baseline had a sensitivity of 57.1%, a specificity of 67.9%, a PPV of 19%, an NPV of 92.3%, and a likelihood ratio of 1.78 for prediction (AUC, 0.597). At week 24, the cutoff of 80% decrease in HBsAg level from baseline had a sensitivity of 71.4%, a specificity of 71.4%, a PPV of 26.3%, an NPV of 94.6%, and a likelihood ratio of 2.50 for prediction (AUC, 0.654).

Profiles of serum HBsAg in patients without HBV DNA reactivation. Among the 62 dually infected patients with undetectable serum HBV at baseline, reappearance of HBV DNA was observed in 21. The baseline serum HBsAg level was not

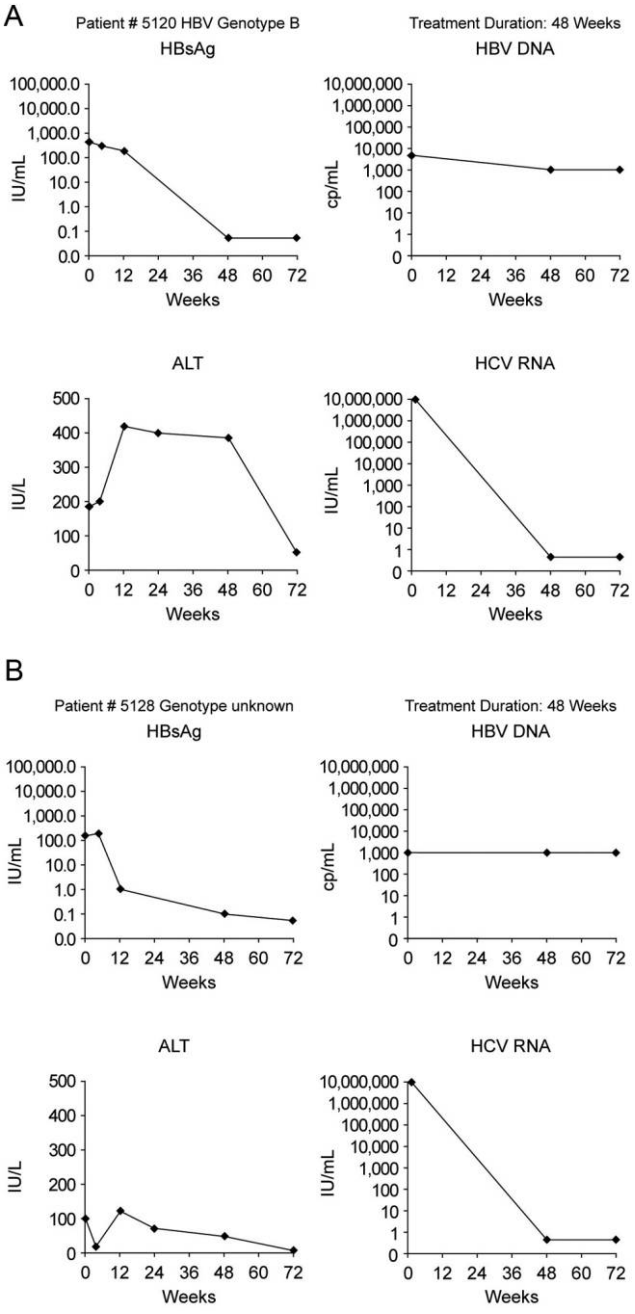

Figure 2. Virologic and biochemical parameters of 2 patients (Patient 5120 and Patient 5128) with baseline high serum hepatitis B surface antigen (HBsAg) level who obtained HBsAg clearance posttreatment. ALT, alanine aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus.

significantly different between the groups of patients with and without HBV DNA reactivation ($P = .563$). Dynamics of serum HBsAg at week 4 also did not correlate with the reactivation of serum HBV DNA posttreatment. Lack of HBV DNA reactivation was associated with HBsAg decrease from baseline to week 12. At week 12 of PEG-IFN therapy, 19 patients showed a decrease of serum HBsAg level >50%, and of these, only 2 (10.5%) developed HBV DNA reactivation. In contrast, 19 (44.2%) of the 43 patients who had a decrease of serum HBsAg level ⩽50% developed reactivation of HBV DNA. Eleven patients showed a decrease of serum HBsAg level >69%. Overall, at week 12, the cutoff of 50% decrease in HBsAg level from baseline had a sensitivity of 41.5%, a specificity of 90.5%, a PPV of 89.5%, an NPV of 44.2%, and a likelihood ratio of 4.37 for the lack of HBV DNA reactivation (AUC, 0.612; 95% confidence interval, 0.469–0.755; $P = .151$). We also examined the predictive value of serum HBsAg level at week 24. We found that the cutoff of 70% decrease in HBsAg level from baseline had a sensitivity of 63.2%, a specificity of 61.9%, a PPV of 75%, an NPV of 48.1%, and a likelihood ratio of 1.66 for the lack of HBV DNA reactivation (AUC, 0.620).

Profiles of serum HBsAg in patients with HBV virologic response. Among the 58 dually infected patients with detectable serum HBV DNA at baseline, 34 patients had an HBV virologic response. Baseline serum HBsAg levels were not significantly different between 2 groups of patients ($P = .558$). At week 12 of PEG-IFN therapy, 28 patients showed a decrease of serum HBsAg level >30%. Among these patients, 22 (78.6%) developed an HBV virologic response. In contrast, only 12 (40%) of the 30 patients who had a decrease in serum HBsAg level of ⩽30% developed an HBV virologic response. At week 12, the cutoff of 30% decrease had a sensitivity of 61.8%, a specificity of 75%, a PPV of 78.6%, a NPV of 60%, and a likelihood ratio of 2.47 for HBV virologic response (AUC, 0.625; 95% confidence interval, 0.469–0.767; $P = .13$). As for the predictive value of serum HBsAg level at week 24, the cutoff of 60% decrease in HBsAg level from baseline had a sensitivity of 68.8%, a specificity of 61.9%, a PPV of 73.3%, a NPV of 56.5%, and a likelihood ratio of 1.81 for HBV virologic response (AUC, 0.613).

DISCUSSION

In our previous study, a defined course of PEG-IFN induced HBsAg clearance in 11.2% of HBeAg-negative patients dually infected with HCV [24]. HBsAg clearance is associated with favorable long-term outcome in patients with CHB and is, therefore, considered to be the ideal end point of therapy [5].

Serum HBsAg level is generally lower in patients with HBeAg-negative CHB than in patients with HBeAg-positive CHB. For example, our recent data revealed that the median serum HBsAg level was 1038 IU/mL (range, 2–11,920 IU/mL) in 100 patients with HBeAg-negative CHB (age, 40–60 years) and was 2380 IU/mL (range, 10–119,330 IU/mL) in 30 patients with HBeAg-positive CHB (age, 40–60 years) (T.-H.S., C.-S. Hsu, C.-L.C., C.-H.L., Y.-W. Huang, T.-C. Tseng, C.-J.L., P.-J.C., M.-Y.L., D.-S.C., and J.-H.K., unpublished data). Other recent studies also demonstrated that the median value of serum HBsAg in patients with HBeAg-negative CHB was about 3 $\log_{10}$ IU/mL [13, 28, 29] (2500 IU/mL in patients with HBeAg-

negative CHB [13] and 1260 IU/mL in patients considered to be in the low replicative phase [28]). In this study, we further demonstrated that the serum HBsAg level in HBeAg-negative CHB patients was even lower if dually infected with HCV, ~1 $\log_{10}$ less than that in HBeAg-negative, HBV-monoinfected patients. Lower HBsAg levels in patients dually infected with HCV and HBV, compared with HBV monoinfection, were also reported recently by Potthoff et al (mean HBsAg level ± standard deviation, 9184 ± 3457 IU/mL for HCV-HBV dual infection and 16,832 ± 4612 IU/mL for HBV monoinfection) [30]. Previous studies revealed that HCV core and NS2 proteins may inhibit replication of HBV and possibly suppress expression of surface gene [31–34]. The reciprocal interactions between HCV and HBV may account for the reduced production of HBsAg in the hepatocytes. Because a low level of HBV replication correlates with favorable treatment outcomes in patients with CHB receiving interferon-based therapy [10], this phenomenon may also explain the relatively high rate of HBsAg clearance posttreatment in our dually infected patients. We found that baseline serum HBsAg level ⩽20 IU/mL correlated with the clearance of HBsAg posttreatment, suggesting that HCV-HBV–coinfected patients with low HBsAg levels represent good candidates for PEG-IFN therapy. In this study, we further demonstrated that serum HBsAg level decreased gradually after treatment. Because some patients with relatively high HBsAg levels also cleared HBsAg, the monitoring of HBsAg can provide a good indication of response to PEG-IFN.

Our original study reported the reactivation of serum HBV DNA in 36.3% of those dually infected patients with undetectable baseline HBV DNA [24]. However, as we demonstrated here, the risk of reactivation was low in inactive carriers if the decrease in serum HBsAg level from baseline to week 12 during therapy was >50% (0.3 $\log_{10}$ IU/mL). Thus, monitoring HBsAg during therapy with PEG-IFN can provide useful information for clinicians.

Although qualitative HBsAg assay has been applied in routine clinical practice as a screening tool for decades, recent data suggest that quantitative determination of HBsAg level may provide a useful insight into the prediction of treatment outcomes with PEG-IFN [11, 15]. These findings are in accordance with the dual antiviral and immunomodulatory effects of PEG-IFN, which result in the suppression of viral replication as well as the clearance of infected hepatocytes. This is supported by the finding that the reduction of serum HBsAg levels parallels the decrease in intrahepatic covalently closed circular DNA [35]. In our study, we found acceptable predictive values of on-treatment serum HBsAg kinetics to predict lack of HBV DNA reactivation and virologic response. Although not strong, the predictive value (90%) of the cutoff of 50% decrease in serum HBsAg at week 12 of therapy for lack of HBV DNA reactivation ensures the physicians and patients that the risk of relapse of hepatitis B activity will be low posttreatment. Moreover, the PPV (79%) of the cutoff of 30% decrease in serum HBsAg at week 12 of therapy for HBV virologic response will encourage the physicians and patients to continue PEG-IFN such that dually infected patients may obtain both HCV sustained virologic response and HBV virologic response.

Clearance of HBsAg in the serum may indicate resolution of chronic HBV infection, or it may just represent the appearance of occult HBV infection. In addition, the correlation of covalently closed circular DNA level in the liver with serum HBsAg level has only been partly clarified in HBeAg-negative patients. For these issues, virologic study of the liver biopsy specimen, including covalently closed circular DNA, would be needed. Unfortunately, the quantitative assay for intrahepatic covalently closed circular DNA has not yet been well established. We, therefore, did not investigate these issues in this study.

In conclusion, HBV-HCV dually infected patients with HBeAg-negative disease have low levels of HBsAg, and the treatment with PEG-IFN plus ribavirin can lead to HBsAg clearance 6 months posttreatment in a high percentage of these patients. Serum HBsAg seems to be a useful on-treatment quantitative marker to predict not only the lack of HBV DNA reactivation but also virologic response in the early phase of PEG-IFN–based therapy in patients with dual chronic hepatitis B and C and may, thus, have a role in the implementation of individualized therapy. Additional large studies are warranted to confirm these data.

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