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【 CASE REPORT 】

Hepatitis B Surface Antigen Decline during Sofosbuvir and Ribavirin Therapy in Hepatitis B Inactive Carriers Who Were Co-infected with Hepatitis C

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Abstract:
Direct-acting antiviral (DAA) therapy carries a potential risk of inducing hepatitis B virus (HBV) reactivation. However, the HBV kinetics during and after DAA therapy in patients co-infected with hepatitis C virus (HCV) and HBV remain unknown. We retrospectively evaluated the HBV kinetics during and after sofosbuvir/ribavirin therapy in four HBV inactive carriers co-infected with HCV. HCV was eradicated in all patients. Changes in HBV-DNA levels during treatment differed among patients. The hepatitis B surface antigen (HBsAg) levels uniformly decreased (mean -0.530 logIU/mL) by the end of treatment and returned to near the baseline in all patients. Sofosbuvir/ribavirin therapy thus demonstrated a suppressive effect on HBsAg.

Key words: hepatitis B virus, hepatitis C virus, sofosbuvir, ribavirin, hepatitis B surface antigen

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Introduction

Hepatitis C virus (HCV) infection is an important public health problem leading to liver cirrhosis and hepatocellular carcinoma. Recent advances in direct-acting antivirals (DAAs) for HCV have dramatically improved the sustained virologic response (SVR) rate.

Hepatitis B virus (HBV) infection is another major cause of chronic liver disease, and co-infections with HBV and HCV are not rare in HBV endemic areas. HBV co-infection does not substantially influence the efficacy of current DAA therapy. However, there is a risk of HBV reactivation following DAA-induced HCV eradication. Current HCV treatment guidelines from the United States, the European Union, and Japan recommend that all patients who initiate DAA therapy be assessed for HBV co-infection by hepatitis B surface antigen (HBsAg) and for previous HBV infection by hepatitis B surface antibody and core antigen (1-3). However, the detailed HBV kinetics during and after DAA therapy in patients co-infected with HCV and HBV remain unknown.

Therefore, we retrospectively examined the HBV kinetics during and after DAA therapy with sofosbuvir and ribavirin in four HBV inactive carriers co-infected with HCV.

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All four patients received sofosbuvir (400 mg) once daily and ribavirin (weight-based dose) twice daily for 12 weeks. All patients had no history of interferon therapy and showed negative findings on a human immunodeficiency virus antibody test before starting DAA therapy.

The HBV status was assessed in all patients by the plasma levels of HBV-deoxyribonucleic acid (DNA), HBV genotype, serum HBsAg, anti-hepatitis B surface antibody (anti-HBs), and hepatitis B envelope antigen (HBeAg) before DAA therapy (Table). Serum HBsAg levels were quantified using the Abbott Architect HBsAg QT assay [Abbott Japan, Tokyo, Japan; lower limit of quantification (LLQ), 0.05 IU/mL]. Plasma HBV-DNA was quantified using the COBAS 6800/8800 system (Roche Diagnostics, Tokyo, Japan; LLQ, 1.0 logIU/mL). HBsAg and HBV-DNA levels were measured at baseline; at weeks 4, 8 and 12 during

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Table. **Patient Characteristics.**

Case	Age	Sex	HCV therapy			HBV status before IFN-free therapy					
			HCV genotype	Liver status	Regimen	Profile	HBsAg (IU/mL)	HBV-DNA (logIU/mL)	HBeAg	HBV genotype	HBV treatment
1	41	M	2A	Chronic hepatitis	SOF/RBV	Inactive career	36.97	2.7	Negative	C	No
2	52	M	2A	Chronic hepatitis	SOF/RBV	Inactive career	29.67	2.1	Negative	C	No
3	67	M	2B	Chronic hepatitis	SOF/RBV	Inactive career	84.62	Undetectable	Negative	C	No
4	70	M	2A	Chronic hepatitis	SOF/RBV	Inactive career	111.00	2.8	Negative	B	No

M: male, HCV: hepatitis C virus, HBV: hepatitis B virus, IFN: interferon, SOF: sofosbuvir, RBV: ribavirin, HBsAg: hepatitis B surface antigen, HBeAg: hepatitis B e-antigen

treatment [end of treatment (EOT)]; at weeks 4, 12, and 24 after treatment; and every 24 weeks after post treatment week 24. We defined HBV reactivation as an increase in HBV-DNA ≥2 logIU/mL from baseline.

None of these patients had received nucleos(t)ide analogue treatment before, during, or after DAA therapy.

Case 1

The patient was a 41-year-old Japanese man co-infected with HBV (genotype C) and HCV [genotype 2A; HCV-ribonucleic acid (RNA), 7.2 logIU/mL]. His pre-DAA therapy HBV assessment findings were as follows: HBeAg, negative; HBsAg level, 36.97 IU/mL; and HBV-DNA level, 2.7 logIU/mL. Therefore, we considered the patient an HBV inactive carrier (Table).

His HCV-RNA level rapidly decreased after starting sofosbuvir and ribavirin therapy and became undetectable in week 4. He finally achieved an SVR without adverse events. The serum HBsAg level decreased during sofosbuvir and ribavirin therapy (-0.629 logIU/mL at the EOT) and returned to near the baseline 4 weeks after treatment (Figure a). The HBV-DNA level also declined during treatment (maximum, -1.5 logIU/mL in week 8) but increased again by the EOT (Figure b). After DAA therapy completion, the HBsAg level gradually decreased by ≥2 logIU/mL. At EOT, the patient achieved HBsAg loss 2.5 years later, and his anti-HBs became positive after 3 years (HBs seroconversion). No ALT flare was observed prior to HBs seroconversion.

Case 2

The patient was a 52-year-old Japanese man co-infected with HBV (genotype C) and HCV (genotype 2A; HCV-RNA, 4.1logIU/mL). His pre-DAA therapy HBV assessment findings were as follow: HBeAg, negative; HBsAg level, 29.67 IU/mL; and HBV-DNA level, 2.1 logIU/mL. Therefore, we considered the patient an HBV inactive carrier (Table). After beginning sofosbuvir and ribavirin therapy, his HCV-RNA level rapidly decreased and became undetectable in week 4. He finally achieved an SVR without adverse events. The patient's serum HBsAg level decreased to -0.314 logIU/mL by the EOT and returned to near the baseline 4 weeks later (Figure a). The HBV-DNA level also declined during treatment (maximum -1.0 logIU/mL in week 4, Figure b). After the completion of DAA therapy, the HBsAg level gradually decreased to -0.903 logIU/mL at post-treatment week 216. No ALT flare was observed after the initiation of DAA therapy.

Case 3

The patient was a 67-year-old Japanese man co-infected with HBV (genotype C) and HCV (genotype 2B; HCV-RNA, 5.9 logIU/mL). His pre-DAA therapy HBV assessment findings were as follows: HBeAg, negative; HBsAg level, 84.62 IU/mL; and HBV-DNA level, undetectable. Therefore, we considered the patient an HBV inactive carrier (Table). After beginning sofosbuvir and ribavirin therapy, his HCV-RNA level rapidly decreased and became undetectable in week 4. He finally achieved an SVR without adverse events. His serum HBsAg levels decreased to -0.706 logIU/mL by the EOT and returned to near the baseline 4 weeks later (Figure a). The HBV-DNA level was undetectable before and throughout DAA therapy (Figure b). Following DAA therapy completion, the HBsAg level gradually decreased by ≥2 logIU/mL (-2.409 logIU/mL in post-treatment week 216). No ALT flare was observed after the initiation of DAA therapy.

Case 4

The patient was a 70-year-old Japanese man co-infected with HBV (genotype B) and HCV (genotype 2A; HCV-RNA, 6.1 logIU/mL). His pre-DAA therapy HBV assessment findings were as follows: HBeAg, negative; HBsAg level, 111.00 IU/mL; and HBV-DNA level, 2.8 logIU/mL. Therefore, we considered the patient an HBV inactive carrier (Table). After beginning sofosbuvir and ribavirin therapy, his HCV-RNA level rapidly decreased and became undetectable four weeks later. He achieved an SVR without adverse events. The patient's serum HBsAg level decreased to -0.470 logIU/mL by the EOT and returned to near the baseline 12 weeks later (Figure a). The patient's HBV-DNA level temporarily declined from the baseline in week 2 but increased again in week 4 (Figure b). No ALT flare was ob-

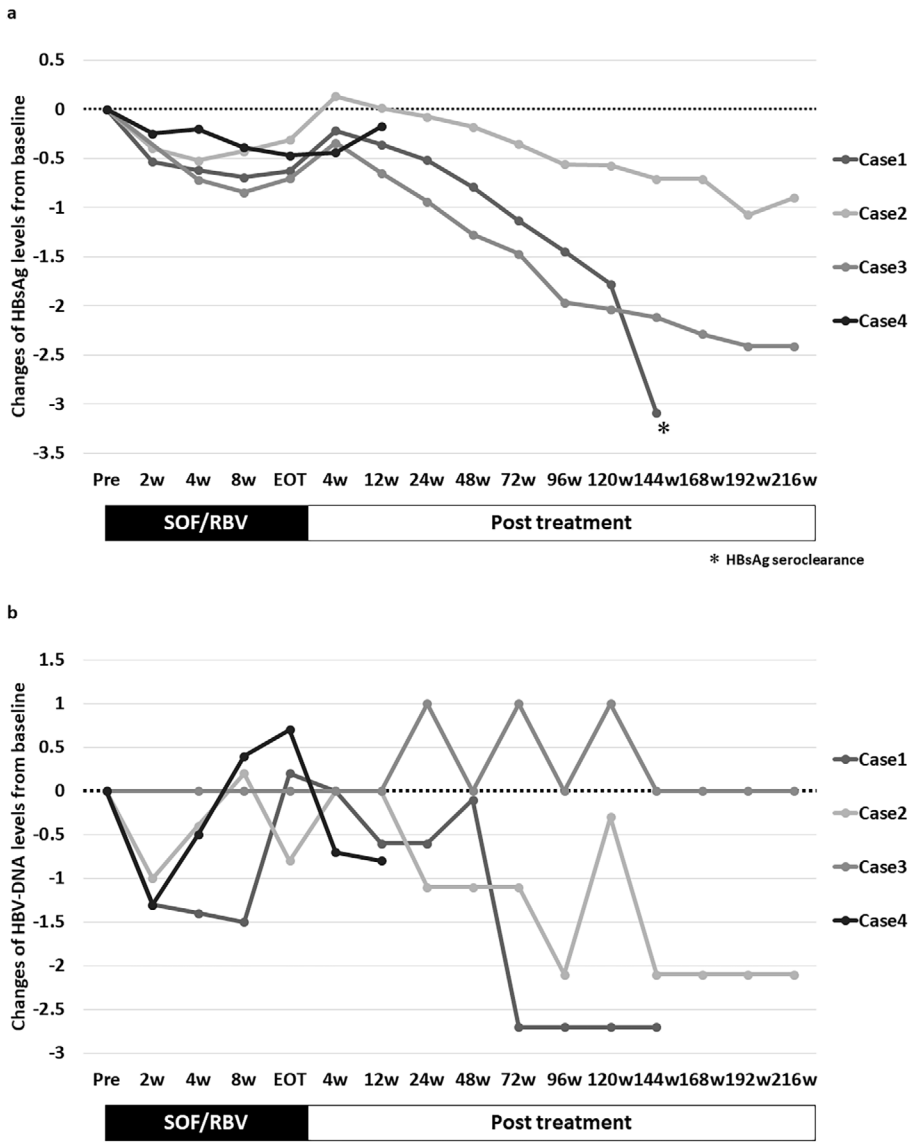

Figure. **a: Serum hepatitis B surface antigen (HBsAg) kinetics in patients receiving sofosbuvir (SOF) and ribavirin (RBV) therapy for hepatitis C virus. The HBsAg levels had uniformly decreased (mean, -0.530 logIU/mL) in all patients by the EOT, and then returned to near the baseline. b: Plasma hepatitis B virus deoxyribonucleic acid (HBV-DNA) kinetics in patients receiving SOF and RBV therapy for hepatitis C virus. The changes in HBV-DNA levels during treatment varied among patients. EOT: end of treatment, w: week**

served after the initiation of DAA therapy.

Discussion

In our patients who were HBV inactive carriers co-infected with HCV, the serum HBsAg levels declined during sofosbuvir and ribavirin therapy (mean -0.530 logIU/mL) and returned to near the baseline after treatment. Interestingly, the impact of HBsAg decline seems greater than that observed in a previous analysis of HBsAg levels during long-term HBV therapy with tenofovir disoproxil fumarate (-0.147 logIU/mL in week 24, -0.208 logIU/mL in week 48) (4). Sofosbuvir is an oral nucleotide polymerase inhibitor of HCV-specific NS5B polymerase and acts as a chain terminator by competing with natural nucleotides, inhibiting HCV-RNA replication (5). Ribavirin is a guanosine analog that interferes with the replication of RNA and DNA viruses and is widely used in anti-HCV therapy combined with interferon or DAAs (6). However, the effect of sofosbuvir and ribavirin on HBV replication is unknown. A previous study of Taiwanese patients co-infected with HBV and HCV also showed that the HBsAg levels declined during DAA therapy and gradually increased after treatment (7). However, no specific DAA regimen showing a suppressive effect on HBsAg was identified in this study. The reason for the decline in HBsAg levels during DAA therapy is unclear. Reportedly, rapid viral clearance following DAA therapy leads to the rebalancing of the innate antiviral response in both

the peripheral blood and liver, such as improving the natural killer cell phenotype and function (8). Based on these findings, the transient decline in HBsAg levels might be associated with the restoration of innate immunity following rapid HCV clearance by DAA therapy.

In co-infected patients, HBV reactivation was sometimes observed after DAA therapy-induced HCV eradication (9, 10); however, this did not occur in our cases for reasons we do not fully understand. A prevoius report showed that HBsAg loss occurred in 10.1% of HBV/HCV co-infected patients treated with DAA therapy, whereas HBV reactivation (HBV-DNA >1 log increase or >100 IU/mL if undetectable at baseline) occurred in 38.0% of patients (7). Interestingly, a sofosbuvir-containing regimen and a low HBsAg level at baseline were negatively associated with HBV reactivation in that study, results that were consistent with the present findings. Sofosbuvir and ribavirin therapy may have affected the HBV status after HCV eradication.

HBsAg loss is currently considered a functional cure and an optimal treatment endpoint in patients with chronic HBV infection (11). However, monitoring the HBsAg decline requires long-term observation, even in patients receiving nucleos(t)ide analogue treatment, which effectively suppresses the reverse transcription of HBV-DNA. Furthermore, HBsAg loss remains extremely rare (12). A previous study revealed that HBs seroconversion in patients co-infected HBV and HCV treated with DAA therapy was associated with low pre-treatment HBsAg (26.3 % and 1.9 % in patients with pre-treatment HBsAg ≤10 IU/mL >10 IU/mL, respectively) (7). In our study, 1 patient with a low baseline HBsAg level (36.97 IU/mL) showed HBs seroconversion 3 years after the EOT. The present findings suggest that sofosbuvir and ribavirin might be a novel therapeutic approach for inducing HBsAg suppression in HBV inactive carriers who are co-infected with HCV.

This study protocol was approved by the Juntendo University Shizuoka Hospital's Ethics Committee, and was performed in accordance with the 2013 revision of the Declaration of Helsinki.

The authors state that they have no Conflict of Interest (COI).

References

1. AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis **67**: 1477-1492, 2018.
2. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol **69**: 461-511, 2018.
3. Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. Japan Society of Hepatology guidelines for the management of hepatitis C virus infection: 2019 update. Hepatol Res **50**: 791-816, 2020.
4. Koike K, Suyama K, Ito H, Itoh H, Sugiura W. Randomized prospective study showing the non-inferiority of tenofovir to entecavir in treatment-naïve chronic hepatitis B patients. Hepatol Res **48**: 59-68, 2018.
5. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med **368**: 34-44, 2013.
6. Hézode C, Bronowicki JP. Ideal oral combinations to eradicate HCV: the role of ribavirin. J Hepatol **64**: 215-225, 2016.
7. Yeh ML, Huang CF, Huang CI, et al. Hepatitis B-related outcomes following direct-acting antiviral therapy in Taiwanese patients with chronic HBV/HCV co-infection. J Hepatol **73**: 62-71, 2020.
8. Serti E, Chepa-Lotrea X, Kim YJ, et al. Successful interferon-free therapy of chronic hepatitis C virus infection normalizes natural killer cell function. Gastroenterology **149**: 190-200.e2, 2015.
9. Chen G, Wang C, Chen J, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: a systematic review and meta-analysis. Hepatology **66**: 13-26, 2017.
10. Mücke MM, Backus LI, Mücke VT, et al. Hepatitis B virus reactivation during direct-acting antiviral therapy for hepatitis C: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol **3**: 172-180, 2018.
11. European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol **67**: 370-398, 2017.
12. 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 **4**: 8-20, 2019.