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# Impact of HBV Infection on Outcomes of Direct-Acting Antiviral Therapy of Chronic Hepatitis C

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## Abstract

**Background:** Most clinical trials of direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection have excluded hepatitis B virus (HBV) coinfection, and little is known about the effects of DAA on chronic hepatitis C patients with HBV coinfection. Recent studies have reported that DAA therapy for HCV can also cause HBV reactivation in patients with HBV and HCV coinfection. The aim of this study was to assess the effects of DAA on sustained virologic response (SVR) and HBV reactivation in patients with chronic hepatitis C. **Methods:** Participants comprised 199 chronic hepatitis C patients who received DAA therapy (96 men, 103 women; mean age,  $66.7 \pm 12.0$  years). **Results:** Twelve patients were coinfecting with HCV and HBV. Sixty patients were HBV surface antigen negative but positive for hepatitis B core antibody and/or hepatitis B surface antibody, and one hundred and twenty-seven patients had not been exposed to HBV. Rates of SVR in HBV and HCV coinfecting patients, HBV prior infection, and no exposure to HBV were 100, 95, and 97%, respectively. Significant differences were seen between each group. No case showed HBV reactivation. **Conclusions:** DAA treatments were effective in patients with HBV coinfection or HBV prior infection, as well as HCV mono-infection. As the number of cases was small, we still suggest caution regarding HBV reactivation in HCV and HBV coinfecting patients undergoing treatment with DAA.

**Keywords:** HBV reactivation, hepatitis C virus, hepatitis B virus, sustained virologic response, direct-acting antiviral

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## 1. Introduction

An estimated 170 million individuals worldwide are infected with hepatitis C virus (HCV), causing chronic hepatitis that can develop into potentially fatal cirrhosis and hepatocellular carcinoma [1]. HCV infection is therefore a major global health problem. Since 1992, interferon (IFN)-based therapies have represented the gold standard of treatment for HCV infection. However, sustained virologic response (SVR) from IFN-based therapy is insufficient for all patients, especially those with HCV genotype 1 or cirrhosis and the elderly. In addition, IFN-based therapy is associated with numerous adverse events, such as fatigue, headache, nausea, insomnia, loss of appetite, influenza-like illness, chills, pyrexia, rash, pruritus, anemia or neutropenia, mental disorder, and thyroid dysfunction. To overcome these problems, IFN-free regimens have been developed and are now becoming the standard of care. Daclatasvir plus asunaprevir was the first IFN-free regimen to become commercially available in Japan for patients with HCV genotype 1b, from 2014 [2]. Several IFN-free regimens have become available for daily practice, and most studies have demonstrated high SVR rates and good safety outcomes [3, 4]. Some IFN-free regimens have demonstrated favorable safety and high efficacy within clinical trials among difficult-to-treat patients such as patients who have experienced DAA treatment, cirrhosis, chronic kidney disease, Human immunodeficiency virus co-infection, those on opiate agonist therapy, and patients with liver transplant [5–10]. However, most clinical trials of IFN-free therapy for chronic hepatitis C have excluded hepatitis B virus (HBV) coinfection. Few questions remain unanswered for IFN-free regimens, but little is known about the effects of DAA on SVR and HBV reactivation among chronic hepatitis C patients with HBV coinfection. Reactivation of HBV in HBV surface antigen (HBsAg)-positive patients treated with immunosuppressive or cytotoxic chemotherapy is well known and has emerged as an important clinical issue [11, 12]. HBV reactivation can be caused not only by immunosuppressive or cytotoxic chemotherapy but also by DAA, with some studies reporting HBV reactivation in patients with HBV and HCV coinfection treated by DAA therapy for HCV [13–16]. In addition, although the risk is low, HBV reactivation in patients with resolved HBV infection—that is, in patients negative for HBsAg but positive for hepatitis B core antibody (HBcAb) and/or hepatitis B surface antibody (HBsAb)—can also occur [17]. HBV reactivation should thus be considered in HCV patients with not only HBV infection but also HBV prior infection treated using DAA therapy. However, little is known about HBV reactivation in chronic hepatitis C patients who have received DAA therapy or the relationship between SVR and HBV coinfection. The aim of this study was to assess the effects of DAA on HBV reactivation in patients with HBsAg-positive status or HBV prior infection, and whether HBV infection affects SVR.

## 2. Methods

### 2.1. Subjects

A total of 199 patients with chronic hepatitis C who had received DAA therapy were enrolled retrospectively, comprising 96 men and 103 women (mean age,  $66.7 \pm 12.0$  years). Patients with Child Pugh classification B and C were excluded. No patient had autoimmune disease or chronic alcohol abuse. Prior to DAA therapy, HBsAg was measured for all patients. Patients showing

HBsAg also underwent measurement of HBsAb and HBcAb. Patients were classified by HBV infection status. Patients with HBs Ag were regarded as HBV + HCV group, and patients were positive for HBcAb and/or HBsAb were regarded as prior infection group, and patients without any of HBsAg, HBcAb, or HBsAb were regarded as no exposure group. Eighty patients were treated with ledipasvir-sofosbuvir, 100 patients were treated using asunaprevir and daclatasvir, and 19 patients were treated with sofosbuvir and ribavirin. Patients who were persistently negative for serum HCV-RNA at 12 weeks after withdrawal of DAA treatment were considered to have shown SVR. Investigation of HBV reactivation was performed during and 12 months after the end of DAA treatment. This study was approved by the Nagoya University Hospital ethics committee. Written informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki.

## 2.2. Statistical analyses

Data are expressed as mean ± standard deviation. Contingency table analysis with Fisher's exact probability test was used for comparisons between groups. Values of  $p < 0.05$  were considered statistically significant. Analyses were conducted using SPSS version 23 software (IBM, New York, NY).

## 3. Results

Twelve patients were positive for HBsAg and defined as showing chronic hepatitis C with HBV coinfection. A total of 187 patients were negative for HBsAg, but 65 patients were positive for HBcAb and/or HBsAb. Five of the sixty-five patients had received HBV vaccination

	HBV + HC N = 12	Prior infection N = 60	No exposure N = 127
Age (y.o.)	64.2 ± 6.8	68.7 ± 9.5	65.7 ± 13.0
Sex: M/F	10/2	30/30	56/71
AST (IU/L)	45.6 ± 36.7	44.3 ± 21.1	49.3 ± 27.0
ALT (IU/L)	56.2 ± 44.1	38.8 ± 19.9	49.4 ± 36.5
Platelet (104/uL)	12.5 ± 5.0	15.2 ± 5.2	15.5 ± 7.1
HCV-RNA level (log IU/mL)	5.9 ± 0.8	6.1 ± 1.1	6.2 ± 0.9
HCV genotype (1/2)	(11/1)	(54/6)	(115/12)
DAA (ASV + DCV/SOF + RBV/LDV + SOF)	(5/1/6)	(28/6/26)	(67/12/48)
SVR	12 (100%)	57 (95%)	123 (97%)
HBV reactivation	none	none	none

HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DAA, direct-acting antiviral; ASV, asunaprevir; DCV, daclatasvir; SOF, sofosbuvir; RBV, ribavirin; LDV, ledipasvir; SVR, sustained virologic response.

**Table 1.** Clinical characteristics.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
Age	66	54	70	61	70	56	70	55	66	69	59	74
Sex	M	M	F	M	M	M	M	F	M	M	M	M
ALT(IU/L)	27	38	164	29	31	87	70	111	19	28	39	31
HCV RNA (log IU/ml)	7.0	5.8	5.7	5.3	5.7	7.1	5.3	4.1	6.3	6.6	5.6	6.2
HCV genotype	2a	1b	1b	1b	1b	1b	1b	1b	1b	1b	1b	1b
Treat for HCV	SOF RBV	ASV DCV	LDV SOF	LDV SOF	LDV SOF	LDV SOF	ASV DCV	LDV SOF	LDV SOF	ASV DCV	ASV DCV	ASV DCV
HBV DNA (log copy/mL)	2.1	0	2.1	2.1	2.8	4.5	0	4.7	3.3	ND	ND	ND
HBs Ag titer (IU/mL)	23	3	43	100	250	3.5	539	63	6	11	11	14
HBeAb	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Treat for HBV	None	ETV	ETV	None	None	ETV	ETV	None	None	None	None	None
HBV genotype	ND	C	ND	ND	ND	B	ND	C	ND	ND	ND	ND
SVR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reactivation	None	None	None	None	None	None	None	None	None	None	None	None

HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DAA, direct-acting antiviral; ASV, asunaprevir; DCV, daclatasvir; SOF, sofosbuvir; RBV, ribavirin; LDV, ledipasvir; SVR, sustained virologic response; ND, not done; ETV, entecavir.

**Table 2.** Clinical characteristics of patients with HBV and HCV coinfection.

and were thus excluded from being considered as showing previous HBV infection; as a result, sixty patients were defined as having prior infection with HBV. The remaining 122 patients were not positive for any of HBsAg, HBcAb, or HBsAb. With the addition of the 5 vaccinated patients, a total of 127 patients were defined as showing no exposure to HBV. Clinical characteristics at baseline and outcomes such as SVR and incidence of HBV reactivation according to HBV infection status are shown in **Table 1**. No significant differences in clinical characteristics including age, sex, alanine aminotransferase, platelet count, HCV genotypes, and HCV viral load were evident between these three groups. SVR rate in HBV and HCV coinfecting patients, HBV prior infection, and no exposure to HBV were 100, 95, and 97%, respectively. No significant differences in SVR were seen between groups. No cases representing definitive HBV reactivation were seen during and after DAA treatment. Clinical characteristics of the 12 patients with HBV and HCV coinfection are shown in **Table 2**. Concentrations of HBsAg were less than 100 IU/mL in most cases, and all titers of HBV-DNA were less than 5 log copies/mL. All patients were positive for hepatitis B e antibody (HBeAb). Four patients received entecavir (ETV) before DAA therapy.

#### 4. Discussion

With the advent of novel agents for chemotherapy and immunotherapy, insufficient data have been accumulated regarding the incidence of HBV reactivation. The association between novel agents and HBV reactivation was noteworthy. At first glance, DAA therapy appears safe, since no HBV reactivation has been observed in several clinical trials. However, most clinical trials of DAA therapy for HCV infection have excluded patients with HBV coinfection, and this bias would obviously mask the incidence of HBV reactivation due to DAA therapy. Real-world experience has revealed HBV reactivation in patients with chronic hepatitis C treated using all-oral direct-acting antiviral regimens [13–16]. In the era of IFN-based therapy against HCV infection, HBV reactivation was not a noteworthy phenomenon for chronic hepatitis C. However, in the era of DAA therapy against HCV infection, HBV reactivation should be a concern in the treatment of patients with HCV infection. IFN rarely induces HBV reactivation, because IFN acts on both HBV and HCV, whereas DAAs act only on HCV. Viral interference between HCV and HBV is known to occur and HCV infection may suppress HBV replication. Rapid eradication of HCV by DAA would thus promote HBV replication and subsequent HBV reactivation. The small number of the total cohort and lack of incidence of HBV reactivation is of major concern for this study. Twelve patients infected with HBV and HCV were observed, and no cases showed definitive HBV reactivation during or after DAA treatment. Wang et al. reported that of 317 patients enrolled, 3 of the 10 patients with HBsAg showed HBV reactivation [18]. However, another study reported no evidence of HBV reactivation among patients treated with ledipasvir-sofosbuvir [19]. HBV reactivation thus remains controversial. Wang et al. speculated that DAAs, particularly NS3 polymerase inhibitors, carry a high risk of HBV reactivation because most reports of HBV reactivation related to DAA involved NS3 polymerase inhibitors [13, 14, 16, 18]. Ledipasvir is a NS5A replication complex inhibitor, and sofosbuvir is a NS5B polymerase inhibitor. The regimen

with ledipasvir-sofosbuvir did not use NS3 polymerase inhibitors, which may be why their study found no cases of HBV reactivation. HBV reactivation induced by ledipasvir-sofosbuvir has been reported, in a patient infected with HIV who was receiving antiretroviral therapy including tenofovir [15]. However, that patient discontinued tenofovir because of osteoporosis 14 months before the onset of HBV reactivation. The effects of discontinuing tenofovir would thus have been relevant in that case. Further studies are needed to clarify whether HBV reactivation may occur irrespective of the class of DAA used. Another hypothesis that could explain the lack of HBV reactivation in this study was that the efficacy of prophylactic treatment with a nucleotide analog in preventing HBV reactivation among patients with HBV infection during and after chemotherapy and immunotherapy is well known. Four of twelve patients had received ETV before DAA therapy in our study and ETV would work as pre-emptive therapy in reducing the incidence of HBV reactivation. A second hypothesis for the absence of HBV reactivation in this study involves HBV status. All patients were negative for hepatitis B e antigen (HBeAg) and HBV-DNA titers were less than 5 log copies/mL. Several risk factors for HBV reactivation have been identified, including HBeAg positivity and high HBV DNA levels [20–22]. Thus, the majority of patients enrolled in our study were low-risk patients with HBeAg-negative status and low titers of HBV DNA.

We did not evaluate HBV genotypes in all patients because of low levels of both HBV DNA and HBsAg, but all our patients were Japanese, and we presumed the most prevalent types would be genotype B or C.

Two billion people have been exposed to HBV worldwide, and our study indicates that one-third of patients with HCV infection were defined as showing prior HBV infection. Most countries perform universal vaccination to prevent HBV infection, but only high-risk groups such as health care workers and household contacts of HBV carriers are selected for HBV vaccination in Japan [23]. Vaccinated patients were easily distinguished from those with resolved HBV infection in this study. Rituximab has become the standard of care for patients with malignant lymphoma, and HBV reactivation has also been reported in lymphoma patients with prior HBV infection [17]. A low level of HBV is well recognized as persisting in the liver and peripheral blood mononuclear cells in patients with resolved HBV infection and a functioning immune system. Immunosuppressive agents or chemotherapy may block the immune functions that suppress HBV replication, thus accelerating HBV replication. HBV reactivation thus occurred in patients with prior HBV infection. The incidence of HBV reactivation in patients with chronic hepatitis C treated by DAAs among patients with prior HBV infection is not yet fully understood, but we speculate that DAAs lead to HBV reactivation in patients with resolved HBV infection. However, we failed to identify any cases representing HBV reactivation among patients with resolved HBV infection in this study. We have previously report a case of acute hepatitis B in a patient with HCV infection after DAA therapy [16]. However, the presence of HBcAb or HBsAb was not determined before DAA therapy, so prior HBV infection status was unclear. This case is speculated to represent HBV reactivation in a patient with previously resolved HBV induced by DAA therapy, based on virologic analysis and clinical status. Amino acid substitutions in the S region as immune escape mutants and minority patterns for HBV genotype and serological subtype were virologic features of HBV reactivation [24, 25]. DAAs were suspected to

induce HBV reactivation, and effective strategies to prevent HBV reactivation are needed. However, data on the incidence of HBV reactivation with DAA therapy are limited. Larger studies are needed to establish whether the risk of HBV reactivation is increased during and after DAA therapy.

Several factors have been identified, including age, liver fibrosis, HCV genotype, HCV RNA levels, race, amino acid substitutions in the core and NS5A regions, and interleukin 28B polymorphisms have been reported as predictors of response to IFN therapy [26–31]. This study investigated whether HBV coinfection affects response to DAA therapy. However, HBV infection was not associated with SVR from DAA therapy. DAA could eradicate over 95% of HCV, and identification of predictors for SVR is difficult. The limitation of the present study was the small sample size, and larger prospective cohorts are needed to confirm our results.

In conclusion, although relatively few cases have been reported in the literature, we suggest caution regarding HBV reactivation in HCV and HBV coinfecting patients undergoing treatment with DAA.

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