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MAJOR ARTICLE

Hepatitis B Virus Reactivation in Patients Receiving Interferon-Free Direct-Acting Antiviral Agents for Chronic Hepatitis C Virus Infection

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Background. Little is known about the risk of hepatitis B virus (HBV) reactivation in patients receiving interferon (IFN)-free direct-acting antiviral agents (DAAs) for hepatitis C virus (HCV).

Methods. Patients who were seropositive for HBV core antibody and who received IFN-free DAAs for HCV were enrolled. Hepatitis B virus reactivation was defined as reappearance of serum HBV deoxyribonucleic acid (DNA) ≥100 IU/mL in patients with baseline undetectable viral load, or ≥2 $\log_{10}$ IU/mL increase of HBV DNA in patients with baseline detectable viral load. Hepatitis B virus-related alanine aminotransferase (ALT) flare was defined as ALT ≥5 times upper limit of normal or ≥2 times of the baseline level. Hepatitis B virus-related hepatic decompensation was defined as presence of jaundice, coagulopathy, hepatic encephalopathy, or ascites.

Results. Compared with no HBV reactivation in 81 HBV surface antigen (HBsAg)-negative patients, 2 of 12 HBsAg-positive patients had HBV reactivation (0% [confidence interval {95% CI}, 0%–4.5%] vs 16.7% [95% CI, 4.7%–44.8%], $P = .015$). No patients had ALT flare or hepatic decompensation. Baseline HBsAg level at a cutoff value of 500 IU/mL was associated with HBV reactivation in HBsAg-positive patients. There was no HBsAg seroreversion in HBsAg-negative patients.

Conclusions. Hepatitis B virus reactivation is limited to HBsAg-positive patients receiving IFN-free DAAs for HCV. Higher baseline HBsAg levels are associated with HBV reactivation. The risk of ALT flares or hepatic decompensation is low in these patients.

Keywords. direct-acting antiviral agent; hepatitis B virus; hepatitis C virus.

Hepatitis C virus (HCV) infection is the leading cause of cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver transplantation [1–3]. Compared with HCV-infected patients who fail to achieve sustained virologic response (SVR) after antiviral therapies, those who achieve SVR have decreased long-term morbidity and mortality [4, 5]. Treatment of HCV by interferon (IFN)-free direct-acting antiviral agents (DAAs) has shown excellent efficacy and safety. Applying IFN-free DAAs has become the current standard of care for the management of HCV infection.

Although treatment with IFN-free DAAs is generally considered to be potent and safe, several case reports have shown that HCV-infected patients who were seropositive for hepatitis B virus (HBV) surface antigen (HBsAg) or isolated HBV core antibody (anti-HBc) developed HBV reactivation after IFN-free DAAs with the presentation of increasing serum HBV viral load, alanine aminotransferase (ALT) elevation, or even hepatic decompensation [6–9]. Based on the case reports, the US Food and Drug Administration and the American Association for the Study of Liver Diseases/Infectious Diseases Society of America posted warning information of potential HBV reactivation for HCV-infected patients receiving IFN-free DAAs [10, 11]. Recently, one study evaluated the risk of HBV reactivation in HCV-infected patients receiving IFN-free DAAs and concluded that HBsAg-positive patients had a higher risk of HBV reactivation than HBsAg-negative patients (30% vs 0%) [12]. However, the incidence and the clinical features of HBV reactivation after IFN-free DAAs for HCV have not been fully addressed by prospective studies. Therefore, we aimed to prospectively evaluate the risk of HBV reactivation in patients receiving IFN-free DAAs for HCV.

METHODS

Patients

Between April 2015 and September 2016, 134 patients who received IFN-free DAAs for HCV were consecutively enrolled

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at the National Taiwan University Hospital (NTUH) and NTUH Yun-Lin Branch. All patients were aged ≥20 years and had chronic HCV infection, defined as detectable HCV antibody ([anti-HCV] Abbott HCV EIA 3.0; Abbott Laboratories, Abbott Park, IL) and serum HCV ribonucleic acid (RNA) (Cobas TaqMan HCV Test version 2.0; Roche Diagnostics GmbH, Mannheim, Germany; limit of quantification, 25 IU/mL) for more than 6 months. In addition, all patients received treatment for 12 weeks and off-therapy follow-up for an additional 12 weeks according to label recommendations. The study was approved by the NTUH Institutional Review Board and was conducted in accordance with the principles of Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. All patients provided written informed consent before participating in the study.

Study Design

This was a prospective cohort study. Baseline demographic data, hemogram, international normalized ratio (INR), serum albumin, serum bilirubin, serum ALT, stage of hepatic fibrosis, anti-HCV, HBsAg (Abbott Architect HBsAg quantification assay; Abbott Laboratories), HBV surface antibody (anti-HBs) (Abbott Architect anti-HBs assay; Abbott Laboratories), anti-HBc (Abbott Architect anti-HBc II assay; Abbott Laboratories), HCV RNA, HCV genotype (Abbott RealTime HCV genotyping II; Abbott Molecular Inc., Chicago, IL), and HBV deoxyribonucleic acid ([DNA] Cobas AmpliPrep/Cobas TaqMan HBV DNA test, version 2.0; limit of detection 12 IU/mL and limit of quantification 20 IU/mL) were assessed before IFN-free DAA treatment [13, 14]. Patients who were seronegative for anti-HBc and who did not complete 12 weeks of IFN-free DAAs were excluded. In addition, Patients were excluded from the study if they received peginterferon or oral nucleos(t)ide analogues that were active against HBV within 24 weeks before the start of IFN-free DAAs.

After IFN-free DAAs, all patients received outpatient visits at weeks 1, 2, 4, 6, 8, and then every 4 weeks until the last visit. The hemogram, INR, albumin, bilirubin, ALT, HBsAg, HBV DNA, and HCV RNA were evaluated at each visit. Hepatitis B virus reactivation was defined as reappearance of serum HBV DNA ≥100 IU/mL in patients with baseline undetectable viral load or ≥2 $\log_{10}$ IU/mL increase of HBV DNA in patients with baseline detectable viral load [15, 16]. Furthermore, we evaluated low-level HBV rebound, defined as reappearance of detectable HBV DNA in patients with baseline undetectable viral load or in those with ≥1 $\log_{10}$ IU/mL increase from baseline detectable viral load. Hepatitis B virus-related ALT flare was defined as ALT ≥5 times upper limit of normal or ≥2 times of the baseline level with concomitant HBV DNA reactivation [15]. Hepatitis B virus-related hepatic decompensation was defined as presence of HBV-related ALT flare and presence of jaundice, coagulopathy, hepatic encephalopathy, or ascites. Patients would receive oral entecavir or tenofovir disoproxil fumarate therapy if they developed HBV-related ALT flare and/or hepatic decompensation during the study. Hepatitis B virus surface antigen seroreversion was defined as reappearance of HBsAg after IFN-free DAA treatment in HBsAg-negative patients.

The risk of HBV reactivation, HBV-related ALT flare, and HBV-related hepatic decompensation were evaluated for all patients who completed 12 weeks of IFN-free DAAs. For patients who had completed off-therapy follow-up for 12 weeks, the risk of off-therapy HBV reactivation and the related clinical events were also evaluated.

Statistical Analyses

Data were analyzed using Statistical Program for Social Sciences (SPSS 17.0; SPSS Inc., Chicago, IL). Patient characteristics were expressed as mean (standard deviation) and percentage when appropriate. The events related to HBV reactivation, ALT flare, hepatic decompensation, and HBsAg seroreversion were shown in numbers and percentages with 95% confidence interval (CI) and were compared by χ^2 with Fisher's exact test when appropriate. All statistical tests were 2-tailed, and the results were statistically significant when a P value was <.05.

RESULTS

Patient Characteristics

Among the 134 enrolled patients, 26 seronegative for anti-HBc were excluded. Of the 108 patients seropositive for anti-HBc, 13 who did not complete 12 weeks of treatment and 2 human immunodeficiency virus (HIV)-infected patients who were seronegative for HBsAg but who receive received nucleos(t)ide reverse-transcriptase inhibitors active against HBV were excluded. Among the 13 patients who did not complete treatment, 1 HBsAg-negative patient developed hepatic decompensation 1 week after paritaprevir/ritonavir, ombitasvir plus dasabuvir (PrOD)-based treatment. The baseline and week-1 HBV DNA levels were undetectable, indicating that this event was not attributed to HBV reactivation. The remaining 12 HBsAg-positive and 81 HBsAg-negative patients were eligible for the study. Furthermore, 86 patients completed off-therapy follow up for 12 weeks (Figure 1). The mean HCV RNA level was 6.2 $\log_{10}$ IU/mL, and 81.7% patients were infected with HCV genotype 1b. With regard to IFN-free DAA regimens, 85.0% of our patients received sofosbuvir (SOF)-based therapies, and the remaining patients received PrOD-based therapies. With regard to HBV serology, 12 (12.9%) patients had HBsAg positivity, 46 (49.5%) had isolated anti-HBc positivity, and 35 (37.6%) had anti-HBs positivity. All HBsAg-negative patients had baseline undetectable serum HBV DNA. For HBsAg-positive patients, 41.7% of them had baseline undetectable serum HBV DNA (Table 1). The baseline HBV viral load ranged from 40 to 282 IU/mL in HBV viremic patients.

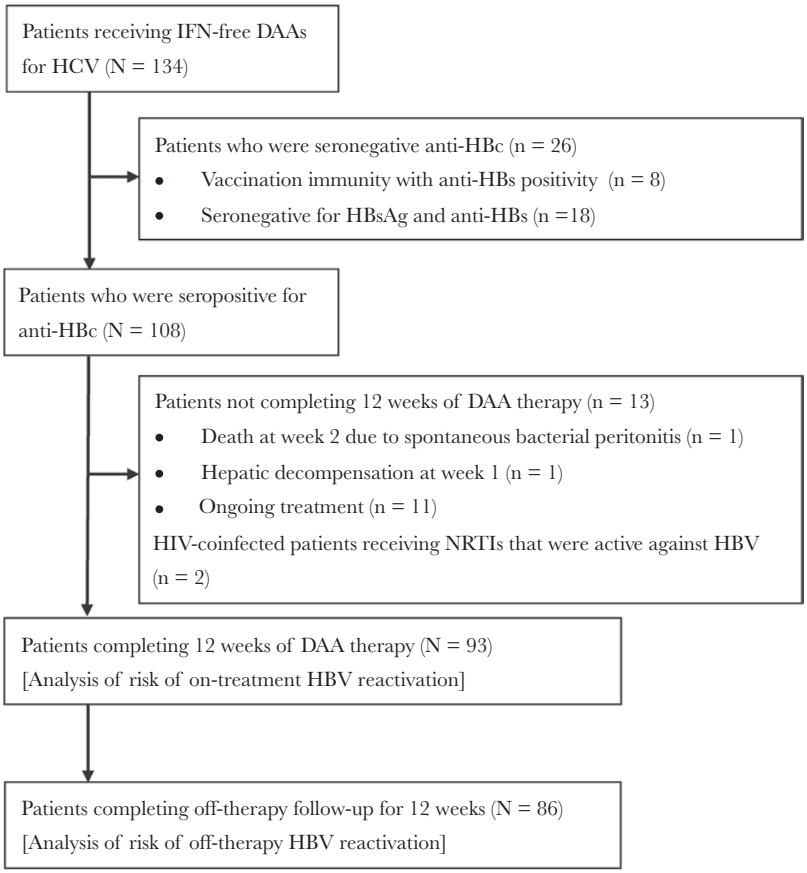

Figure 1. Study flow diagram.

Risks of Hepatitis B Virus Reactivation After Interferon-Free Direct-Acting Antiviral Agents

Table 2 shows the incidence of HBV reactivation and reactivation-related clinical events in patients completing IFN-free DAAs. None of 81 HBsAg-negative patients and 2 of 12 HBsAg-positive patients developed HBV reactivation (0% [95% CI, 0%–4.5%] vs 16.7% [95% CI, 4.7%–44.8%], $P = .015$). Neither patients with isolated anti-HBc positivity nor patients with anti-HBs positivity had HBV reactivation (0% [95% CI, 0%–7.7%] and 0% [95% CI, 0%–9.9%], respectively). Neither of the 2 HBsAg-positive patients with HBV reactivation developed ALT flare or hepatic decompensation. No HBsAg-negative and 6 HBsAg-positive patients developed low-level HBV rebound (0% [95% CI, 0%–4.5%] vs 50% [95% CI, 25.4%–74.6%], $P < .0001$). In addition, there was no HBsAg seroreversion in HBsAg-negative patients. During the off-therapy follow up, there were no additional events in terms of HBV reactivation, ALT flare, or hepatic decompensation.

Hepatitis B Virus Deoxyribonucleic Acid and Hepatitis B Surface Antigen (HBsAg) Dynamics in HBsAg-Positive Patients

Table 3 shows the dynamic changes of serum HBV DNA and HBsAg levels in HBsAg-positive patients receiving IFN-free DAAs. Two patients had on-treatment HBV reactivation. Patient No. 3 was a 66-year-old treatment-naive HCV genotype 1b-infected woman who had stage F2 fibrosis. Her baseline HBV DNA level was undetectable. She had intermittent HBV viremia (peak level: 190 IU/mL at week 4 of treatment) after ledipasvir plus SOF therapy. The baseline ALT level was 179 U/L. The ALT level was 64 U/L after 1 week of treatment and the levels were <30 U/L after 2 weeks of treatment. Patient No. 11 was a 49-year-old HCV genotype 1b-infected man who relapsed from prior peginterferon/ribavirin therapy and who had stage F3 fibrosis. The baseline HBV DNA was 40 IU/mL. The HBV DNA level increased after ledipasvir plus SOF plus therapy, and the viral load peaked at week 4 of treatment (29 900 IU/mL). Subsequent HBV DNA levels during off-therapy follow up ranged from 810 to 23 200 IU/mL. The baseline ALT level was 58 U/L, and the ALT levels were <30 U/L after 1 week of treatment. Both patients did not receive organ transplantation or immunosuppressive agents or had HIV coinfection.

With regard to HBsAg dynamics, the HBsAg levels decreased during DAA therapies and rebounded after stopping treatment in all patients. Furthermore, the changes of HBsAg levels were not correlated to the HBV dynamics. The baseline HBsAg levels of the 2 patients with HBV reactivation were 844.5 and 585.74 IU/mL, respectively. The HBsAg levels were less than 500 IU/mL in the remaining 10 patients without HBV reactivation.

Table 1. Baseline Patient Characteristics

Characteristics	HBsAg (+), n = 12	Isolated Anti-HBc (+), n = 46	Anti-HBs (+), n = 35	Overall, N = 93
Age (year), mean (SD)	55 (9)	56 (8)	57 (9)	56 (8)
Male, n (%)	6 (50.0)	24 (52.2)	16 (45.7)	46 (49.5)
Prior Peg-IFN/RBV failure, n (%)	6 (50.0)	25 (54.3)	17 (48.6)	48 (51.6)
HCV RNA, $\log_{10}$ IU/mL, mean (SD)	6.0 (2.3)	6.4 (2.4)	6.3 (2.5)	6.2 (2.2)
HCV Genotype, n (%)				
1a	0 (0)	1 (2.2)	1 (2.9)	2 (2.2)
1b	10 (83.3)	38 (82.6)	28 (80.0)	76 (81.7)
2	2 (16.7)	7 (15.2)	6 (17.1)	15 (16.1)
HCV Treatment Regimen, n (%)				
LDV/SOF	5 (50.0)	23 (50.0)	18 (51.4)	46 (49.5)
LDV/SOF + RBV	2 (20.0)	9 (19.6)	7 (20.0)	18 (19.4)
SOF + RBV	2 (16.7)	7 (15.1)	6 (17.1)	15 (16.1)
PrOD	2 (16.7)	5 (10.9)	4 (11.4)	11 (11.8)
PrOD + RBV	1 (8.3)	2 (4.3)	0 (0)	3 (3.2)
Undetectable HBV DNA, n/n (%)[a]	5 (41.7)	0 (0)	0 (0)	5 (5.4)
METAVIR Fibrosis Stage, n (%)[b]				
F0/F1	3 (25.0)	12 (26.1)	9 (25.7)	24 (25.8)
F2	3 (25.0)	10 (21.7)	12 (34.3)	25 (26.9)
F3	1 (8.3)	6 (13.0)	3 (8.6)	10 (10.8)
F4	4 (33.3)	16 (34.8)	11 (31.4)	31 (33.3)
Undetermined	1 (8.3)	2 (4.3)	0 (0)	3 (3.2)
Hemoglobin, g/dL, mean (SD)	14.0 (2.6)	14.4 (2.4)	14.2 (2.3)	14.1 (2.9)
White blood cell count, 10^9/L, mean (SD)	5320 (2258)	5532 (2698)	5038 (2379)	5226 (2587)
Platelet count, 10^9/L, mean (SD)	168 (54)	162 (62)	165 (58)	166 (58)
INR, mean (SD)	0.98 (0.08)	1.03 (0.07)	1.02 (0.12)	1.01 (0.10)
Albumin, g/dL, mean (SD)	4.4 (1.5)	4.2 (1.8)	4.4 (1.7)	4.3 (1.7)
Total bilirubin, mg/dL, mean (SD)	0.8 (0.6)	2.2 (1.5)	1.2 (0.7)	2.5 (2.3)
Direct bilirubin, mg/dL, mean (SD)	0.3 (0.2)	1.2 (0.8)	0.5 (0.3)	1.1 (1.0)
ALT, U/L, mean (SD)	92 (62)	84 (72)	105 (85)	102 (78)

Abbreviations: ALT, alanine aminotransferase; anti-HBc, hepatitis B virus core antibody; anti-HBs, hepatitis B virus surface antibody; DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface agent; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; IQR, interquartile range; LDV, ledipasvir; LOD, limit of detection; Peg-IFN, peginterferon; PrOD, paritaprevir/ritonavir/ombitasvir/dasabuvir; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir.

[a]Determined by Cobas AmpliPrep/Cobas TaqMan HBV DNA test, version 2.0 with LOD of 12 IU/mL.

[b]Determined by transient elastography (Fibroscan; Echosens, Paris, France) according to the cutoff values proposed by Castéra et al [14]. Two HBsAg-negative patients and 1 HBsAg-positive patient had unreliable examination with less than 10 valid measurements, a successful rate of less than 60%, and the IQR more than 30% of the median liver stiffness measurement value.

DISCUSSION

Our study demonstrated the following findings: (1) no HBV reactivation was observed in HBsAg-negative patients receiving IFN-free DAAs for HCV [12, 17]; (2) the HBV reactivation was limited to HBsAg-positive patients, but there were no HBV-related ALT flare and/or hepatic decompensation; (3) there was no additional risk of HBV reactivation after stopping DAA treatment for HCV, which was frequently observed in HBsAg-positive patients receiving immunosuppressive agents [15, 16].

Table 2. Incidence of HBV Reactivation and Clinical Events in Patients Receiving IFN-Free DAA Therapy

IFN-Free DAA Treatment Status	HBV Serology			HBV Reactivation, n/N (%)	HBV-Related ALT Flare, n/N (%)	HBV-Related Hepatic Decompensation, n/N (%)	HBsAg Seroreversion, n/N (%)
	HBsAg	Anti-HBs	Anti-HBc				
Patients completing 12 weeks of therapy (N = 93)	+	–	+	2/12 (16.7)	0/12 (0)	0/12 (0)	-
	–	–	+	0/46 (0)	0/46 (0)	0/46 (0)	0/46 (0)
	–	+	+	0/35 (0)	0/35 (0)	0/35 (0)	0/35 (0)
Patients completing 12 weeks of off-therapy follow-up (N = 86)	+	–	+	2/12 (16.7)	0/12 (0)	0/12 (0)	-
	–	–	+	0/43 (0)	0/43 (0)	0/43 (0)	0/43 (0)
	–	+	+	0/31 (0)	0/31 (0)	0/31 (0)	0/31 (0)

Abbreviations: ALT, alanine aminotransferase; anti-HBc, hepatitis B virus core antibody; anti-HBs, hepatitis B virus surface antibody; DAA, direct-acting antiviral agent; HBsAg, hepatitis B surface agent; HBV, hepatitis B virus; IFN, interferon.

Table 3. Dynamic Changes of Serum HBV DNA and HBsAg in HBsAg-Positive Patients[a]

Patient No.	HBV Marker	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	SVR_4	SVR_8	SVR_{12}	First Time Point of On-Treatment Undetectable HCV RNA
1	HBV DNA	TND	TND	TND	TND	TND	TND	TND	TND	TND	Week 4
	HBsAg	62.42	42.81	33.57	32.48	27.55	24.38	41.98	46.52	48.31	
2	HBV DNA	201	162	115	30	99	TND	30	TND	46	Week 4
	HBsAg	16.22	5.89	6.00	3.89	3.98	2.34	19.51	21.56	35.76	
3	HBV DNA	TND	TND	31	190	73	TND	TND	48	122	Week 2
	HBsAg	844.5	605.32	398.82	421.30	208.58	201.68	228.42	352.37	445.67	
4	HBV DNA	TND	TND	TND	TND	29	TND	TND	TND	TND	Week 4
	HBsAg	44.36	32.22	24.54	21.93	29.00	15.09	20.93	18.56	12.06	
5	HBV DNA	TND	TND	TND	TND	TND	TND	TND	TND	TND	Week 2
	HBsAg	72.56	56.87	49.52	44.43	40.53	39.82	63.68	70.53	76.79	
6	HBV DNA	156	182	253	332	1650	1128	829	1024	747	Week 4
	HBsAg	412.35	398.45	352.58	298.54	284.57	266.79	351.56	376.89	384.09	
7	HBV DNA	141	203	717	1740	1900	1520	1740	1900	1520	Week 1
	HBsAg	98.82	87.71	69.90	69.26	37.43	29.22	33.23	49.67	57.30	
8	HBV DNA	TND	TND	TND	53	27	TND	TND	28	TND	Week 2
	HBsAg	108.73	97.12	133.15	21.93	72.97	42.70	89.83	109.67	104.69	
9	HBV DNA	282	143	122	54	108	46	155	453	864	Week 2
	HBsAg	253.42	211.49	192.84	145.32	132.58	122.79	175.62	189.17	203.87	
10	HBV DNA	62	36	TND	52	27	TND	181	84	74	Week 2
	HBsAg	185.67	175.70	133.68	118.91	132.58	121.53	151.32	189.65	185.62	
11	HBV DNA	40	146	818	29 900	1220	351	810	5420	23 200	Week 4
	HBsAg	585.74	439.07	208.62	246.35	128.51	92.76	229.2	304.04	357.98	
12	HBV DNA	177	155	241	264	651	303	519	486	529	Week 2
	HBsAg	11.9	6.39	7.69	6.82	4.06	4.17	20.12	20.89	18.75	

Abbreviations: DNA, deoxyribonucleic acid; HBsAg, hepatitis B surface agent; HBV, hepatitis B virus; HCV, hepatitis C virus; LOD, limit of detection; LOQ, limit of quantification; RNA, ribonucleic acid; SVR, sustained virologic response; TND, target not detected.

[a]HBV DNA determined by Cobas AmpliPrep/Cobas TaqMan HBV DNA test, version 2.0 with LOD of 12 IU/mL and LOQ of 20 IU/m, and HBsAg determined by Abbott Architect HBsAg quantification assay (IU/mL), respectively.

In recent studies, several case reports indicated that patients who were seropositive for HBsAg or isolated anti-HBc experienced HBV reactivation and its clinical events after IFN-free DAAs for HCV, raising the concerns for HBV monitoring and prophylactic use of oral anti-HBV agents [6–9]. Our study was in line with the Wang et al [12] report that the risk of HBV reactivation was significantly higher in HBsAg-positive patients compared with HBsAg-negative patients. Although the risk of HBV reactivation in HBV-positive patients was comparable between our (16.7% [95% CI, 4.7%–44.8%]) and the Wang et al [12] studies (30.0% [95% CI, 10.8%–60.3%]), we did not observe any HBV-related ALT flare or hepatic decompensation. Furthermore, there was no ALT elevation before or at the peak of HBV DNA levels in HBsAg-positive patients with HBV reactivation, indicating that on-treatment ALT monitoring may not be sensitive enough to detect HBV reactivation.

With regard to HBsAg-negative patients, our study was also in line with the Wang et al [12] report that none developed HBV reactivation after IFN-fee DAAs for HCV. In addition, none of our HBsAg-negative patients developed HBsAg seroreversion, which was frequently observed in those receiving anti-CD20 or hematopoietic stem cell transplantation [15]. Although 1 case report describing a patient with isolated anti-HBc seropositivity developed HBV reactivation and hepatic decompensation after IFN-free DAAs, the presence of anti-HBc immunoglobulin M and HBsAg may indicate HBV superinfection rather than HBV reactivation [9, 18].

Although the HBV DNA dynamics in our HBsAg-positive patients were poorly correlated to the HBsAg dynamics, the HBsAg levels decreased during IFN-free DAAs and rebounded after stopping treatment. The baseline HBsAg levels of 2 patients with HBV reactivation were numerically higher than those of the remaining 10 patients without HBV reactivation. The clinical relevance of HBsAg dynamics to HBV reactivation in HBsAg-positive patients receiving IFN-free DAAs are still unclear. Further studies are needed to explore the potential mechanisms.

Our study had 2 limitations. First, the number for HBsAg-positive patients was small, and more patients should be evaluated to confirm the dynamic changes of serum HBV DNA/HBsAg levels and the clinical events in these patients. Second, our HBsAg-positive patients were all inactive HBV carriers (HBV DNA level <2000 IU/mL). The risk of HBV reactivation and the clinical events in active HBV carriers await more studies.

CONCLUSIONS

In conclusion, HBsAg-negative patients receiving IFN-free DAAs for HCV have a low risk of HBV reactivation. In contrast, HBsAg-positive patients receiving IFN-free DAAs for HCV have a significantly higher risk of HBV reactivation, although the risk of HBV-related ALT flare or hepatic decompensation is low. Whether baseline HBsAg levels can predict HBV reactivation after IFN-free DAAs need further confirmation.

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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