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Hepatitis due to Reactivation of Hepatitis B Virus in Endemic Areas Among Patients With Hepatitis C Treated With Direct-acting Antiviral Agents

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Hepatitis due to reactivation of hepatitis B virus (HBV) has been reported in patients treated with direct-acting antiviral (DAA) agents for chronic hepatitis C virus infection. We performed an observational study to determine the incidence of and factors associated with hepatitis in 327 patients receiving pan-oral DAA agents for HCV infections in areas endemic for HBV in China. Ten patients were positive for hepatitis B surface antigen (HBsAg), and 124 patients had occult HBV infection. HBV reactivation was determined by measuring HBV DNA and HBsAg status in serial serum samples collected every 2 weeks during DAA treatment and then every 4 weeks after treatment until week 12. In the total study population, 10 patients (3.1%) had hepatitis; 3 cases were associated with HBV reactivation (1 case not in the icteric phase, 1 case in the icteric phase, and 1 case with liver failure) and 7 from other causes. Testing positive for HBsAg before DAA treatment was a strong risk factor for developing hepatitis during treatment (hazard ratio, 15.0; $P < .001$).

Keywords: Therapy; Risk Factor; Coinfection; Prognostic Factor.

Globally, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the most common causes of liver diseases.[1] Because of the similar mode of transmission, coinfection with HBV and HCV is common in HBV endemic areas. In China, coinfection of HBV in patients with chronic HCV infection has been estimated to be as high as 8.4%.[2] Importantly, HBV-HCV coinfection is associated with more severe liver diseases and with a higher prevalence of liver cancer.[3] In addition, the prevalence of occult HBV infection (OBI), defined by the presence of HBV DNA in the absence of hepatitis B surface antigen (HBsAg), has been estimated to range widely from 11.9% to 44.4% in HCV-infected patients.[4] Numerous studies have evaluated the clinical manifestations of occult or serologically silent HBV infection in the setting of chronic hepatitis C (CHC), and the results are conflicting. Most studies reported the association of OBI with more severe hepatic inflammation and outcomes such as cirrhosis and hepatocellular carcinoma (HCC).[5]

Recently, concerns have been raised regarding the occurrence of hepatitis due to HBV reactivation in CHC patients coinfected with HBV after treatment with pan-oral direct-acting viral agents (DAAs). To date, 5 such cases have been reported, with 1 case also coinfected with human immunodeficiency virus. All 4 non–human immunodeficiency virus coinfected cases had genotype 1 CHC and received protease inhibitor–containing pan-oral DAAs with either simeprevir or asunaprevir.[6–8] The case with human immunodeficiency virus coinfection had genotype 4d HCV, which was treated with sofosbuvir and ledipasvir in addition to highly active antiretroviral therapy containing etravirine, raltegravir, and darunavir/ritonavir.[9] These cases of hepatitis due to HBV reactivation not only occurred in HBsAg-positive chronic hepatitis B patients but also in HBsAg-negative patients with OBI. Each case of hepatitis occurred during DAA therapy, and all patients achieved sustained virologic response (SVR) despite HBV reactivation. The occurrence of these events has recently prompted the European Medicines Agency to assess the extent of hepatitis B reactivation in patients treated with DAAs for HCV and to evaluate whether any measures are needed to optimize the treatment.[10]

With the increased use of pan-oral DAA therapy for CHC in Asia where the prevalence of HBsAg positivity and

Abbreviations used in this paper: CHC, chronic hepatitis C; DAA, direct-acting antiviral agent; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IP-10, interferon γ–induced protein 10; OBI, occult HBV infection; SVR, sustained virologic response.

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OBI is high, it is of great importance to understand the true incidence and risk factors for hepatitis due to hepatitis B reactivation in these patients. In our present study, we examined prospectively the incidence of hepatitis due to HBV reactivation in a cohort of Chinese patients with CHC infection that was treated with pan-oral DAAs.

Methods

In this prospective observational cohort study, we evaluated 327 consecutive Chinese adults treated with pan-oral DAAs including ledipasvir/sofosbuvir (Harvoni; Gilead Sciences Inc, Branford, CT), daclatasvir (Daklinza; Bristol-Myers Squibb, Wallingford, CT)/sofosbuvir (Sovaldi; Gilead Sciences), and ombitasvir /paritaprevir/ritonavir plus dasabuvir (Viekira Pak; AbbVie, Worcester, MA) from June 2014 to July 2015 at the Humanity and Health Medical Centre, Hong Kong Special Administrative Region, China. None of these CHC patients with positive HBsAg were on anti-HBV therapy. Before treatment, plasma HCV RNA level, HCV genotype and subtype, and liver stiffness were measured. In addition, serum samples from all patients were tested for HBV DNA level and HBV-specific antigens and antibodies. Patients were

Table 1. Demographic and Clinical Characteristics of 327 CHC Patients Treated With Pan-oral DAAs

		HBsAg negative		
	HBsAg positive N = 10	OBI N = 124	Non-OBI N = 193	*P* value
Age, *y*[a]				.051[b]
Median (range)	51 (41–61)	54 (20–75)	50 (20–83)	
Male[c] sex, n (%)	7 (70.0)	69 (55.6)	99 (51.3)	.44
Body mass index (kg/m^2)[a]				.10[d]
Median (range)	24.2 (19.7–27.9)	24.2 (17.6–30.6)	23.4 (15.3–34.5)	
HCV RNA (log_{10} *IU/mL*)				
Median, log_{10} *IU/mL*[a]	6.6 (0.7)	6.5 (2.3)	6.5 (1.3)	.81
>6,000,000 IU/mL,[c] n (%)	4 (40.0)	49 (39.5)	63 (32.6)	.40
HCV genotype[c]				
GT1a/GT2a/GT3a/GT6 (%)	60/40/0/0	83.9/16.1/0/0	79.3/16.6/3.1/1.0	.12
HBV DNA (log_{10} *IU/mL*)	3.2 (2.0)			
HBV genotype B/C	6/4			
HBV BCP/PC mutation, median (range)				
BCP A1762-T%	100 (20–100)			
BCP G1764-A%	100 (28–100)			
PC G1896-A%	100 (100–100)			
Previous treatment,[c] n (%)				.004
Experienced	4 (40.0)	99 (79.8)	130 (67.4)	
Naive	6 (60.0)	25 (20.2)	63 (32.6)	
Previous response,[c] n (%)				.001
Relapser	3 (75.0)	65 (65.7)	76 (58.5)	
Null response	0 (0.0)	25 (25.2)	17 (13.1)	
Intolerant	1 (25.0)	9 (9.1)	37 (28.5)	
Interleukin 28B genotype,[c] n (%)				.47
CC	7 (70.0)	72 (58.1)	131 (67.9)	
CT	3 (30.0)	48 (38.7)	57 (29.5)	
TT	0	4 (3.2)	5 (2.6)	
Interferon L4,[c] n (%)				.33
TT/TT	7 (70.0)	85 (70.2)	141 (74.2)	
ΔG/TT	2 (20.0)	34 (28.1)	42 (22.1)	
ΔG/ΔG	1 (10.0)	2 (1.6)	7 (3.7)	
Fibrosis stage (METAVIR),[c] n (%)				.30
F0-F1 (LSM ≤7.3 kPa)	3 (30.0)	28 (22.6)	67 (34.7)	
F2 (7.3 kPa < LSM ≤9.7 kPa)	0 (0.0)	11 (8.9)	19 (9.8)	
F3 (9.7 kPa <LSM ≤14.7 kPa)	1 (10.0)	13 (10.5)	17 (8.8)	
F4 (LSM >14.7 kPa)	6 (60.0)	72 (58.1)	90 (46.6)	
Cirrhosis,[c] n (%)	6 (60.0)	72 (58.1)	90 (46.6)	.11
ALT (*U/L*)[a]	58.5 (60.9)	57 (45.0)	52 (61.9)	.66
AFP[a]	6.7 (124.8)	8 (45.2)	5.7 (70.7)	.24

NOTE. Data are shown as (%), median (range).
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BCP, basic core promoter; GT, genotype; LSM, liver stiffness measurement; PC, precore.
[a]Significance was tested by Kruskal-Wallis rank test, corrected by Dunn's test for multiple comparison between groups.
[b]Significant difference between OBI and non-OBI group, $P = .022$.
[c]Significance was tested by Fisher exact test.
[d]Significant difference between OBI and non-OBI group, $P = .049$.

followed biweekly during treatment and every 4 weeks after the end of treatment for 12 weeks, and their clinical parameters and serum HCV RNA levels were measured at each visit. For patients who had hepatitis and those who had OBI, all serially collected serum samples were tested for HBsAg and HBV DNA level. Reporting of this study conforms to the STROBE statement. The conduct of this study was in compliance with the Declaration of Helsinki and approved by the local Ethics Committee. Informed consent was obtained from the patients for the use of collected clinical data and serum samples.

Hepatitis was defined as more than 2-fold increase of serum alanine aminotransferase on 2 consecutive determinations at least 5 days apart from the nadir during DAA therapy and follow-up. Reactivation of past HBV infection was defined as one of the following: (1) HBsAg turning from negative to positive, (2) appearance of HBV DNA in absence of HBsAg, and (3) HBV DNA turned from undetectable to detectable in HBsAg-negative patients.

Differences among 3 groups were compared by the Kruskal-Wallis rank test for continuous variables and the Fisher exact test for categorical variables. The Cox proportional hazards model was used to compare differences in the rate of occurrence of hepatitis between groups by obtaining hazard ratios and 95% confidence intervals, with adjustment of possible clinical factors. Significance level was set to $P < .05$. Statistical analyses were done with STATA (Stata Corp, College Station, TX).

Results

Among 327 Chinese patients with CHC infection, ten (3.1%) were HBsAg positive (all hepatitis B e antigen [HBeAg] negative and hepatitis B e antibody [anti-HBe] positive). One hundred twenty-four of the 317 HBsAg-negative patients (39.1%) had OBI. There were no differences in HCV genotype, HCV viral load, and degree of liver fibrosis among HBsAg-positive patients and HBsAg-negative patients with or without OBI (Table 1).

SVR at 12 weeks after the end of treatment was achieved in all patients except 1 genotype 1b patient with cirrhosis who had viral breakthrough at week 12 and was subsequently diagnosed to have HCC. Apart from hepatitis, no significant serious adverse events were reported in all patients treated with DAAs.

Three of the 10 HBsAg-positive patients (30%) had hepatitis, 1 anicteric, 1 icteric, and 1 with hepatic failure, and all were related to HBV reactivation (Table 2). Seven HBsAg-negative patients (2.2%) (3 patients with OBI and 4 patients without OBI) had hepatitis during DAA therapy, but none were caused by HBV reactivation, with 4 related to intake of herbs, 2 related to binge of alcohol, and 1 with unknown cause. The incidences of hepatitis and hepatitis due to HBV reactivation were significantly higher in HBsAg-positive patients than in HBsAg-negative patients ($P = .01$). With Cox proportional hazards analysis, HBsAg positivity was predictive of hepatitis (hazard ratio, 15.0; $P < .001$).

Discussion

Recently, concerns have been raised regarding hepatitis due to HBV reactivation after successful clearance of HCV with pan-oral DAAs in HBV/HCV coinfected patients.[10] To our knowledge, this study represents the largest single cohort of Chinese patients treated with pan-oral DAAs.

Table 2. Hepatitis Among 327 CHC Patients Treated With Pan-oral DAAs

		HBsAg negative		
	HBsAg positive N = 10	OBI positive N = 124	OBI negative N = 193	*P* value[a]
Hepatitis				.003
No	7 (70.0)	121 (97.6)	189 (97.9)	
Yes	3 (30.0)	3 (2.4)	4 (2.1)	
	n = 3	n = 3	n = 4	
Median time to onset of hepatitis, *wk* (range)[b]	8 (4–10)	8 (2–12)	4 (4–12)	.90
Severity of hepatitis				.60
Anicteric	1 (33.3)	3 (100)	4 (100)	
Icteric	1 (33.3)	0 (0.0)	0 (0.0)	
Hepatic failure	1 (33.3)	0 (0.0)	0 (0.0)	
Cause of hepatitis				.01
HBV reactivation	3 (100.0)	0 (0.0)	0 (0.0)	
TCM/other medications	0 (0.0)	1 (33.3)	3 (75.0)	
Alcohol	0 (0.0)	2 (66.7)	0 (0.0)	
Others or unknown	0 (0.0)	0 (0.0)	1 (25.0)	

TCM, traditional Chinese medicine.
[a]Significance was tested by Fisher exact test.
[b]Significance was tested by Kruskal-Wallis rank test.

The underlying mechanisms of HBV reactivation during pan-oral DAA therapy for CHC remain speculative. Previously, several reports have documented that de novo HCV superinfection in the setting of chronic hepatitis B can result in HBeAg seroconversion and in some cases, clearance of HBsAg.[11,12] This suggests that HCV infection can suppress HBV replication, but the detailed mechanism is not clear. New insights have been made available from cell culture studies, where HBV and HCV were shown to be able to replicate in the same hepatocyte without evidence of interference.[13] This suggests that HCV suppresses HBV replication via an indirect mechanism. The recent observation is also consistent with this finding, in which there was an overexpression of interferon-stimulated genes and also interferon γ–induced protein 10 (IP-10) in HBV/HCV coinfected patients with HCV dominance, and the level of IP-10 inversely correlated with the decline of HBsAg.[14] This shows that HCV can suppress HBV replication by host immune responses. Hence, clearance of HCV infection with effective anti-HCV therapy could then ameliorate immune control on HBV replication and result in HBV reactivation. This is also in keeping with the finding that rapid reduction of HCV viral load in CHC patients treated with DAA could downregulate hepatic expression of type II and III interferons, their receptor and interferon-stimulated genes,[15] and normalize overactivated interferon-sensitive innate immune cells such as natural killer cells.[16]

In analogy to patients with OBI treated with intense immunosuppressive therapy,[17,18] life-threatening fulminant hepatitis due to HBV reactivation has also been reported in CHC patients with OBI treated with NS3/4A protease inhibitors–containing regimen.[6] However, in our study none of the patients with OBI experienced HBV reactivation because the majority of patients were not treated with NS3/4A protease inhibitors–containing regimens. Previously, HCV NS3/4A protease inhibitors have been implicated to affect the restoration of innate immune responses within infected cells by inactivating 2 important signaling molecules in the sensory pathways that react to HCV pathogen-associated molecular patterns to induce interferons, ie, the mitochondrial antiviral signaling protein and the Toll-IL-1 receptor domain–containing adaptor-inducing interferon-β.[19]

In our study, less than one-third of HBsAg-positive patients had hepatitis due to HBV reactivation with the treatment of pan-oral DAA therapy. This is lower than that observed in HBsAg-positive patients receiving chemotherapy for hematologic or solid malignancies, where the pooled (range) incidence of HBV reactivation, HBV-related hepatitis, HBV-related liver failure, and HBV-related death was reported to be 37% (24%–88%), 33% (24%–88%), 13% (5%–33%), and 7% (0%–63%), respectively.[20] This suggested that the removal of suppressive effect of HCV by DAAs on HBV replication is not as potent as the removal of immunosuppressive effect in patients treated with intense chemotherapy or immunosuppressive therapy.

In conclusion, hepatitis due to HBV reactivation is substantially increased in those CHC patients who are also HBsAg positive and are treated with pan-oral DAAs therapy. Hence, it is of great clinical importance to check HBsAg status before initiating pan-oral DAAs therapy, especially in HBV endemic areas.

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