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Hepatitis B Virus Infection and Hepatitis C Virus Treatment in a Large Cohort of Hepatitis C–Infected Patients in the United States

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For the Chronic Hepatitis Cohort Study Investigators

Dear Editors

The rare emergence of hepatitis B virus (HBV) reactivation among hepatitis C virus (HCV)-infected patients receiving direct-acting antiviral (DAA) therapy raises questions about how many HCV-infected patients have active, past, or latent/occult HBV co-infection, and their

Conflicts of interest

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DAA treatment experience[1–3] We sought to characterize these factors, including possible post-DAA reactivation, among HCV patients in the Chronic Hepatitis Cohort Study (CHeCS), a “dynamic” observational study conducted at 4 large integrated U.S. health care systems. Study methods have been described elsewhere.[4]

Among 14,099 HCV-diagnosed patients still alive and infected in 2014, we analyzed DAA treatment and HBV serologic and DNA assays performed as part of routine clinical care at any time in the patient’s history through the end of 2016. (Ongoing DAA treatment ascertainment for 2016 was still pending and unavailable for 1143 cohort patients [8.1%].) We reviewed all alanine aminotransferase (ALT) values during the 12 months after the initiation of therapy for elevation.

The prevalence of hepatitis B surface antigen (HBsAg)/HBV DNA and total hepatitis B core antibody (anti-HBc) positivity varied by demographics including gender, race, and age (Table 1). Among 14,695 HCV patients, 10,551 (74.8%) had been tested for HBsAg and/or HBV DNA and of these 115 (1.1%) had ≥1 positive test (Table 1). In these patients with a positive test for HBsAg and/or HBV DNA, 26 (22.6%) had only 1 positive test (thus, chronic vs acute infection status could not be confirmed) and 42 (36.5%) had become HBsAg/HBV DNA negative by 2016; the remaining 47 (40.9%) had confirmed chronic HBV infection with positive tests for HBsAg and/or HBV DNA ≥6 months apart. Among 13,984 patients without a positive test for HBsAg or HBV DNA, 5298 (37.9%) were tested for anti-HBc and of these 2136 (40.3%) were positive, indicating possible prior infection (Table 1). Among all total anti-HBc positive persons, 788 (14.9% of those tested) were “isolated” anti-HBc positive, with negative HBsAg and negative anti-HBs, indicating either possible resolved infection with waning antibody levels, occult infection, or a false-positive test. In the 11,848 HCV patients (84.0%) without prior/current HBV infection (no positive tests for HBsAg/HBV DNA or anti-HBc), 5999 (50.6%) were tested for hepatitis B surface antibody (anti-HBs), and of these 1923 (32%) were positive indicating immunity (Table 1). Among patients negative or not tested for markers of HBV infection or immunity the majority (7745, or 54.9% of the cohort) did not have record of any HBV vaccination in electronic health record data.

Across the entire cohort, 3836 (27.2%) had received DAA therapy (Table 1). The proportions achieving a sustained virologic response (SVR; about 90%) and with post-DAA ALT elevations were similar across groups. Among the 115 patients ever HBsAg or HBV DNA positive, 25 (21.7%) were treated and of these 1 (4.0%) was identified as having a single ALT level above the upper limit of normal during the 4–52 weeks after therapy initiation. Among these DAA-treated patients, pretreatment HBV disease activity was infrequently measured, but when data were available the HBV DNA level was low (Table 1, footnote). Only 7 ever-HBsAg/DNA positive patients (28.0%) who received DAA therapy had HBV DNA testing after therapy initiation. Of these, 5 (62.5%) were DNA negative or below the test lower limit of detection both before and after therapy and 2 (28.6%) had low levels of HBV DNA (Table 1, footnote).

Among the 2136 anti-HBc–positive/HBsAg-negative patients, 663 (31.0%) were DAA treated. In these treated patients, 84 (12.7%) had post-DAA initiation HBsAg testing and

none were positive (Table 1). Among treated patients with post-DAA ALT data available, 61 (10.6%) of those with SVR and 26 (50.0%) of those without SVR had ≥1 ALT level above the upper limit of normal during the 4–52 weeks after therapy initiation (Table 1). During this period, none of these patients exhibited a pattern of normalized ALT followed by elevation that might point to reactivation, although 4 patients who achieved SVR experienced a doubling or more of ALT.

We subsequently reviewed the medical records of the subset of patients with laboratory evidence of past or current HBV infection who achieved SVR and had elevated post-DAA ALT levels during the year after treatment initiation that were ≥50% increased over the most recent pretreatment level. No HBsAg/DNA-positive patients met these criteria. Among the 26 total anti-HBc–positive/HBsAg-negative patients meeting these criteria, none had evidence that the increase was attributed to reactivation. However, only 10 (38.5%) were tested for HBsAg after therapy initiation, including 5 of the 7 experiencing recent liver transplant-related complications. One patient tested HBsAg negative during the year after therapy but subsequently underwent liver transplantation and tested HBsAg positive, indicating likely immunosuppression-related reactivation. Another received chemotherapy, tested HBV DNA negative, and began HBV prophylactic therapy. Other conditions associated with the ALT increases included complications of preexisting decompensated cirrhosis, surgery, a transient ischemic attack, and possible side effects of high-dose ibuprofen or antibiotic therapy.

In summary, although a small proportion (1%) of all HCV patients were ever positive for HBsAg and/or HBV DNA, indicating active infection, almost 40% of those tested had evidence of past resolved HBV infection (anti-HBc positive), although by 2016 a majority of the cohort (62%) had not had recommended anti-HBc testing. About one-half the cohort did not have evidence of immunity to HBV by anti-HBs results; of note, the Advisory Committee on Immunization Practices recently approved language clarifying that all patients with HCV infection are recommended for hepatitis B vaccination.[5]

About one-quarter of all patients received DAA therapy; elevations in ALT after DAA initiation were uncommon among patients achieving SVR. No cases of DAA-associated reactivation were detected, but post-treatment HBsAg/HBV DNA testing was rarely performed. As per 2016–2017 updates to American Association for the Study of Liver Diseases/Infectious Diseases Society of America treatment guidelines (available at: www.hcvguidelines.org), all patients initiating HCV DAA therapy should be assessed for current or past HBV infection with HBsAg, anti-HBs, and anti-HBc to determine the potential for rare but serious post-therapy reactivation of HBV. The presence of active or resolved HBV infection should not be an impediment to HCV therapy.

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Table 1

HBV Testing, DAA Treatment Status and Outcomes among 14,099 Patients Living With Chronic HCV Infection, 2016

		Hepatitis B Tests		
	n	**HBsAg and/or HBV DNA**	**Anti-HBc**	**Anti-HBs**
Total	14,099	10,551 tested	5,298 tested	5,999 tested
Demographic characteristics	n (column %)	Ever test positive (acute or chronic HBV infection[a]) (row %)	Test positive (past HBV infection) (row %)	Test positive (HBV immune) (row %)
		115 (1.1)[a]	2136 (40.3)	1923 (32.1)
Gender				
Male	8322 (59.0)	82 (1.3)	1489 (43.9)	1074 (30.5)
Female	5777 (41.0)	33 (0.8)	647 (33.9)	849 (34.2)
Age group (y) at last follow-up				
≤30	811 (5.8)	1 (0.2)	4 (2.8)	200 (71.9)
31–40	1197 (8.5)	13 (1.4)	44 (15.8)	204 (44.8)
41–50	1734 (12.3)	24 (1.9)	164 (27.4)	234 (30.8)
51–60	5059 (35.9)	37 (1.0)	686 (35.9)	596 (26.8)
>60	5298 (37.6)	40 (1.0)	1238 (52.3)	689 (30.2)
Race				
Asian	558 (4.0)	12 (2.5)	139 (34.8)	86 (26.9)
Black, non-Hispanic	3119 (22.1)	30 (1.2)	748 (55.7)	501 (36.3)
White, non-Hispanic	8986 (63.7)	63 (1.0)	1048 (34.8)	1135 (31.3)
Other	1436 (10.2)	10 (1.0)	201 (36.8)	201 (30.1)
Clinical characteristics	n (column %)	n (column %)	n (column %)	n (column %)
Ever history of cirrhosis[b]				
Yes	4286 (30.4)	44 (38.2)	986 (46.2)	581 (30.2)
No	9813 (69.6)	71 (61.8)	1150 (53.8)	1342 (69.8)
DAA treatment?[c]	3836 (27.2)	25 (21.7)[d]	663 (31.0)	496 (25.8)
Among DAA treated, post-treatment testing for HBsAg and/or HBV DNA?	327 (8.5)	9 (37.0)[e]	84 (12.7)	60 (12.1)

		Hepatitis B Tests		
	n	HBsAg and/or HBV DNA	Anti-HBc	Anti-HBs
Among patients with testing				
Test positive	6 (1.8)	5 (55.6)	0	1 (1.7)
Test negative	321 (98.2)	4 (44.4)	84 (100)	59 (98.3)
DAA treatment response[f]				
SVR	3202 (91.5)	20 (95.2)	565 (91.5)	399 (86.9)
No SVR	297 (8.5)	1 (4.8)	52 (8.5)	60 (13.1)
ALT elevation above ULN during the 4–52 weeks after DAA initiation?[f]				
Patients with SVR				
No ALT elevation	2282 (71.3)	12 (60.0)	400 (70.8)	298 (74.7)
ALT elevation, <2 times ULN	213 (6.7)	1 (5.0)	43 (7.6)	15 (3.8)
At least one ALT >2 times ULN	118 (3.7)	0	19 (3.4)	16 (4.0)
Unknown	589 (18.4)	7 (35.0)	103 (18.2)	70 (17.5)
Patients without SVR				
No ALT elevation	103 (34.7)	1 (100)	15 (28.9)	20 (33.3)
ALT elevation, <2 times ULN	68 (22.9)	0	14 (26.9)	16 (26.7)
At least one ALT >2 times ULN	63 (21.2)	0	12 (23.1)	10 (16.7)
Unknown	63 (21.2)	0	11 (21.2)	14 (23.3)

ALT, alanine aminotransferase; DAA, direct-acting antiviral; anti-HBc, total core antibody; anti-HBs, surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; SVR, sustained virologic response; ULN, upper limit of normal.

[a]Among those ever HBsAg or DNA positive: 42 (36.5%) had lost HBsAg by end of observation, 47 (40.9%) had confirmed chronic HBV, and 26 (22.6%) had insufficient data to confirm chronic infection status.

[b]Cirrhosis defined as having ≥1 of the following: biopsy stage F4, FIB-4 score of >5.88, and/or *International Classification of Disease, 9th edition,* codes indicating cirrhosis, hepatic decompensation, liver failure, hepatic encephalopathy, portal hypertension, esophageal varices and/or ascites.

[c]Among all DAA-treated patients, 197 (5.1%) were retreated with >1 course of DAA therapy, including 1 of 25 (4.0%) treated with a history of HBsAg positivity, 35 anti-HBc–positive (5.3%), and 38 total anti-HBs–positive (7.7%) persons treated. Overall, 67.9% of patients were treated with ledipasvir/sofosbuvir (Harvoni), 20.2% with sofosbuvir (Solvadi) and ritonavir or simeprevir, 4.5% simeprevir (Olysio), 4.2% sofosbuvir/velpatasvir (Epclusa), 3.3% dasabuvir/ombitasvir/paritaprevir/ritonavir (Viekira pak), 2.2% daclatasvir (Daklinza), 0.5% elbasvir and grazoprevir (Zepatier), and 0.2% ombitasvir/paritaprevir/ritonavir (Technivie).

[d]Of 25 ever-HBsAg/DNA–positive patients who received DAA therapy, 8 (32%) had converted to HBsAg/HBV DNA-negative before treatment; of the remaining 17 patients, only 6 (35%) had a HBV DNA measurement within the 3 years before treatment and of these 2 were qualitatively positive and the remainder had HBV viral loads of 13, 97, 406, and 5029 IU/mL.

[e] Among the 25 ever-HBsAg/DNA–positive patients who received DAA therapy, only 7 (28.0%) had HBV DNA testing after therapy initiation. Of these, 5 (62.5%) were DNA negative or below the test lower limit of detection before and after therapy, 1 (12.5%) was positive on a qualitative test before treatment and had a DNA level of 378 IU/mL at most recent test performed 8 months after therapy, and 1 had nearly identical levels of HBV DNA before (13 IU/mL) and at the most recent test 1 month after (17 IU/mL) therapy.

[f] Response to DAA therapy and post-therapy ALT levels unknown or pending for 337 treated patients (8.8%), including 4 (16%) ever-HBsAg/DNA positive, 46 (6.9%) anti-HBc positive/HBsAg negative, and 37 (7.5%) anti-HBs positive patients.