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MAJOR ARTICLE

Absence of HBV Reactivation in Patients With Resolved HBV Infection Following DAA Therapy for Hepatitis C: A 1-Year Follow-up Study

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Background. Patients with chronic hepatitis C virus (HCV) infection and active or previous hepatitis B virus (HBV) are at risk of HBV reactivation (HBV-R) during direct-acting antiviral (DAA) therapy. Recent reports suggest that HBV-R may even occur several months after completion of DAA therapy. The aim of this study was to assess the risk of HBV-R in patients with resolved HBV after successful DAA therapy during long-term follow-up (FU).

Methods. Among 848 patients treated for chronic HCV, all patients with resolved HBV and long-term FU data were eligible for inclusion. Patients were HBV DNA/hepatitis B surface antigen (HBsAg)–negative at the end of therapy (EOT) and were followed for up to 52 weeks thereafter. Patients underwent regular alanine transaminase (ALT) testing, and additional HBV DNA/HBsAg testing was performed at FU week 12, end of FU, and in case of an ALT increase above the upper limit of normal (>ULN).

Results. A total of 108 patients were followed up for a mean (range) of 41.5 (24–52) weeks after EOT. None of the patients experienced reverse HBsAg seroconversion or reappearance of HBV DNA. One patient received a liver transplantation; 1 patient was diagnosed with de novo hepatocellular carcinoma, and 2 patients died. Eighteen patients (16.7%) had increased ALT levels (grade 0/1). Of those, the majority were male (72.2%) and significantly more patients had cirrhosis (66.7% vs 36.2%, $P = .015$) or received ribavirin as part of their treatment regimen (86.7% vs 46.8%, $P = .041$). None of these were associated with HBV-R.

Conclusions. Our results indicate that the risk of HBV-R in patients with resolved HBV treated with DAAs for HCV is low during long-term follow-up.

Keywords. hepatitis B virus; hepatitis C virus; HBV reactivation; HCV treatment; direct-acting antivirals; long-term follow-up.

The introduction of direct-acting antivirals (DAAs) has revolutionized the treatment of chronic hepatitis C virus (HCV) infection, and a sustained virologic response (SVR) can now be achieved in the majority of patients [1]. Following the approval of interferon-free DAA regimens, several cases of hepatitis B virus (HBV) reactivation prompted both the European Medicine Agency's Pharmacovigilance Risk Assessment Committee (PRAC) and the US Food and Drug Administration (FDA) to issue warnings about possible HBV reactivation (HBV-R) during DAA therapy [2, 3]. HBV-R may occur in both patients with active (hepatitis B surface antigen [HBsAg]–positive) and resolved (HBsAg-negative/hepatitis B core antibody [HBcAb]–positive) HBV infection. Patients with active HBV coinfection are at greater risk of HBV-R compared with those with resolved infection (24% vs 1.4%) [4]. The occurrence of HBV-R during DAA treatment in patients with resolved HBV is particularly noteworthy as this has primarily been associated with B-cell-depleting agents (eg, rituximab) [5]. Importantly, although active HBV/HCV coinfection is relatively rare in developed countries, HBcAbs are present in up to one-third of the HCV-infected population [6].

Several studies focused on assessing HBV-R during DAA therapy, as the majority of HBV-Rs were reported within 4–8 weeks from the start of antiviral therapy. However, recent case reports suggest that HBV-R may occur up to 50 weeks after the end of treatment (EOT) [7, 8]. Moreover, Serper and colleagues reported that considerable alanine transaminase (ALT) elevations and clinically significant hepatic events were more frequent after DAA therapy than during DAA therapy in a large US veterans cohort [9]. So far, no systematic study has been performed evaluating the long-term risk of HBV-R after DAA therapy in patients with resolved HBV infection. HBV-R could potentially have harmful consequences, as the majority of patients are not routinely followed beyond 12 weeks after completion of therapy (FU12) in the absence of advanced liver fibrosis or cirrhosis.

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The aim of the present study was to systematically assess the long-term risk of HBV-R- and HBV-R-related hepatitis in patients with resolved HBV infection after successful HCV eradication with interferon-free DAA therapy.

METHODS

Study Cohort and Surveillance Parameters

All consecutive patients who presented to our outpatient clinic for treatment of chronic HCV infection were eligible for study inclusion. Patients were required to have resolved HBV infection (HBsAg-negative/HBcAb-positive), to have completed DAA therapy with SVR12, and to be followed regularly in our outpatient clinic beyond 12 weeks after EOT. To detect any clinically relevant HBV-R during follow-up, strict inclusion criteria were applied with regard to surveillance of ALT and additional HBV DNA and HBsAg testing from stored blood samples:

1) Patients had to undergo regular ALT testing (at FU12, the end of follow-up, and every 12–24 weeks in between) until a maximum of 52 weeks after EOT. To account for variability of clinical visits and timing of lab draws in clinical practice, a 2-week interval before and after the calculated visits post-EOT was allowed.
2) Patients were known to have resolved HBV infection at baseline (HBsAg-negative/HBcAb-positive) and known to be HBsAg- and HBV DNA–negative at the end of treatment, as described previously [10]. For this study, additional testing of HBsAg and HBV DNA was required from stored blood samples in every patient at week 12 after EOT and at the end of follow-up. In patients who experienced an increase in ALT levels above the upper limit of normal (males >50U/L, females >35 U/L) during follow-up, additional testing for HBsAg and HBV DNA was performed at ALT peak.

As this was a real-world cohort with patient visits at the treating physician's discretion, not all eligible patients fulfilled the strict surveillance criteria for a total of 1 year after EOT, and they were therefore were reclassified into one of the following three groups if complete data were available for (a) 24 weeks of follow-up, (b) 36 weeks of follow-up, and (c) 1 year of follow-up (48–52 weeks). Patients who did not fulfill either of these criteria were excluded from this study.

Pediatric patients (aged <18 years) or patients with HIV coinfection, patients on any antiviral therapy or prophylaxis apart from DAA therapy to treat HCV, and patients with a history of liver or any other organ transplantation or on immunosuppressive therapy were excluded from this analysis.

The study was approved by the local ethics committee of the Goethe University Frankfurt (vote #43/18).

Patient Characteristics

Patient characteristics and laboratory results at baseline and end of follow-up were retrospectively and anonymously analyzed from electronic hospital charts.

Diagnosis of cirrhosis was based on histology from liver biopsy (if available) or the combination of clinical and noninvasive imaging (including ultrasound, transient/shear-wave elastography, and magnetic resonance imaging), in combination with typical laboratory findings (ie, liver function tests, platelet count). HCV genotype was determined as described previously [10]. Transaminase elevations were graded according to the Acquired Immune Deficiency Syndrome Clinical Trials Group: grade 0: <1.25× upper limit of normal (ULN); grade 1 (mild): 1.25–2.5× ULN; grade 2 (moderate): 2.5–5 ULN; grade 3 (severe): 5–10× ULN; grade 4 (life-threatening) >10× ULN [11].

Determination of Serologic and Molecular HBV Parameters

For testing of HBV serologic markers, the Abbott ARCHITECT platform (Abbott Diagnostics, Lake Forest, IL) was employed. For HBV DNA quantification, the COBAS AmpliPrep/COBAS TaqMan HBV DNA assay, version 2.0 (Roche Diagnostics, Pleasanton, CA) was used according to the manufacturer's instructions. The COBAS AmpliPrep/COBAS TaqMan HBV DNA assay has a lower limit of quantification of 20 IU/mL.

HBV-R was defined as any reverse HBsAg seroconversion (patients who were HBsAg-negative at baseline and who became HBsAg-positive during follow-up) or any quantifiable HBV DNA (≥20 IU/mL) during the study period. HBV-R-related hepatitis was defined as HBV-R in combination with ALT concentrations of 2 or more times above the ULN [4].

Statistics

The statistical analysis program bias, version 11.03 (Epsilon-Verlag, Darmstadt, Germany), was used for all statistical analyses. Descriptive statistics are shown as mean +/- SD or median and range. Group differences in baseline parameters between patients were calculated using the nonparametric Mann-Whitney *U* test (continuous variables) or the Fisher exact/chi-square test (categorical variables), as appropriate. A *P* value <.05 was considered statistically significant.

RESULTS

A total of 848 patients received different DAA-based regimens for chronic HCV infection in the outpatient clinic of our tertiary care reference center between January 2014 and July 2016. Overall, 263 patients were HBcAb-positive and HBsAg-negative. A total of 108 patients who were followed for up to 52 weeks after EOT were included (mean follow-up [range], 41.5 [24–52] weeks) Figure 1. A total of 33, 13, and 62 patients had complete surveillance data for 24 weeks, 36 weeks, and 48–52 weeks after EOT, respectively. One

hundred fifty-five patients were excluded as they had insufficient long-term follow-up data or did not achieve SVR. Among the 108 included patients, 62 (57.4%) were male with a median age (range) of 58 (18–86) years, 74 (68.5%) had genotype 1 infection, and 57 patients (52.8%) had previously received interferon-based therapy. Cirrhosis was diagnosed in 44 patients (40.7%). Forty-six patients (42.6%) were known to be hepatitis B surface antibody–positive, though not all patients were tested. Detailed patient characteristics are shown in Table 1.

In 18 patients (16.3%), an ALT elevation above the ULN was detected at least once during 1-year follow up. One patient underwent liver transplantation, 1 patient was diagnosed with de novo hepatocellular carcinoma, and 2 patients died during the follow-up period.

HBV Reactivation

All patients were HBV DNA–negative and HBsAg-negative at the end of treatment, and all patients, including those who experienced ALT elevations, remained HBV DNA– and HBsAg-negative during follow-up (FU12 and end of follow-up testing). In patients who experienced ALT elevations, neither regular testing nor testing at ALT peak revealed reverse HBsAg seroconversion or detectable HBV DNA.

ALT Elevations

Among the 18 patients with documented ALT elevations above the ULN, the majority were male (72.2%) and the median age (range) was 57 (41–67) years. Twelve patients (66.6%) had HCV genotype 1 infection. There were significantly more patients with cirrhosis in the group of patients with elevated ALT than

Table 1. Patient Characteristics and Baseline Parameters of All Included Patients With SVR12 and Long-term Follow-up

Characteristics	All Patients (n = 108)	Patients Without ALT Elevation During FU (n = 90)	Patients With ALT Elevation During FU (n = 18)	*P* Value
Age, median (range), y	58 (18–86)	58 (18–86)	57 (41–67)	
Male sex, No. (%)	62 (57.4)	49 (54.4)	13 (72.2)	.13
Ethnicity, No. (%)				
Europe/Caucasian	97 (89.8)	80 (88.9)	17 (94.4)	
Middle East	8 (7.4)	7 (7.8)	1 (5.6)	
Central Asia	2 (1.9)	2 (2.2)	0	
East Asia	1 (0.9)	1 (1.1)	0	
HCV genotype, No. (%)				
1a and other/unknown GT1 subtypes	37 (34.3)	31 (34.4)	6 (33.3)	
1b	37 (34.3)	31 (34.4)	6 (33.3)	
2	7 (6.5)	6 (6.7)	1 (5.6)	
3	18 (16.7)	15 (16.7)	3 (16.7)	
4, 5, 6, and mixed genotypes	9 (8.3)	7 (7.8)	2 (11.1)	
Cirrhosis, No. (%)	44 (40.7)	32 (35.6)	12 (66.7)	.015
Prior treatment experience with IFN, No. (%)	57 (52.8)	47 (52.2)	10 (55.6)	
HCV RNA, mean (range), $\log_{10}$ IU/mL	6.6 (4.2–7.8)	6.6 (4.2–7.8)	6.4 (5.3–7.0)	
ALT, mean ± SD, U/L	79 ± 51	76 ± 51	92 ± 49	.21
Bilirubin, mean ± SD, mg/dL	0.8 ± 0.8	0.8 ± 0.8	1.0 ± 0.7	.22
Creatinine, mean ± SD, mg/dL	0.9 ± 1.1	0.8 ± 0.5	1.4 ± 2.3	.64
INR, mean ± SD	1.05 ± 0.15	1.05 ± 0.16	1.06 ± 0.08	
HBsAb status, No. (%)	46 (42.6)	37 (41.1)	9 (50.0)	.33
HCV treatment				
LDV, SOF ± RBV	53 (49.1)	46 (51.1)	7 (38.9)	
OBV/PTV + RBV	4 (3.7)	4 (4.4)	0 (0)	
OBV/PTV + DSV ± RBV	20 (18.5)	15 (16.7)	5 (27.8)	
SMV, SOF ± RBV	4 (3.7)	4 (4.4)	0 (0)	
DCV, SOF ± RBV	18 (16.7)	14 (15.6)	4 (18.5)	
SOF + RBV	8 (7.4)	7 (7.8)	1 (5.6)	
Other	1 (0.9)	0 (0)	1 (5.6)	
RBV-based regimen	55 (50.9)	42 (46.7)	13 (86.7)	.041
Outcome until end of follow-up				
No adverse event	104 (96.3)	87 (96.7)	17 (94.4)	
De novo HCC	1 (0.9)	1 (1.1)	0 (0)	
Liver transplantation	1 (0.9)	1 (1.1)	0 (0)	
Death	2 (1.9)	1 (1.1)	1 (5.6)	

Abbreviations: ALT, alanine transaminase; DCV, daclatasvir; FU, follow-up; HBsAb, hepatitis B surface antibody; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

in those without ALT elevations (66.7% vs 35.6%, P = .015). There was no difference with regard to DAA treatment regimens between groups. However, significantly more patients with ALT elevations had received additional ribavirin for HCV eradication (86.7% vs 46.7%, P = .041).

When applying the commonly used grading system by the Acquired Immune Deficiency Syndrome Clinical Trials Group, 12 patients (66.7%) had grade 0 ALT elevations and 6 patients (33.3%) had grade 1 ALT elevations. No moderate (grade 2), severe (grade 3), or life-threatening (grade 4) ALT elevations were observed in this patient cohort.

The natural course of ALT elevations during follow-up is shown in Supplementary Figure 1. Seven patients had elevated ALT levels already at EOT, and 1 normalized during follow-up. The majority of patients with ALT elevations during FU had normal ALT levels at EOT. The most likely reasons for ALT increase were concomitant nonalcoholic fatty liver disease (n = 10) and alcoholic liver disease (n = 1). Two patients with cirrhosis developed elevated ALT levels during a severe systemic infection, and 1 of them died. The other 5 patients all had known liver cirrhosis, but no plausible cause for ALT elevations could be identified.

DISCUSSION

In this study, we investigated the risk of HBV-R during 1 year of follow-up in patients with resolved HBV infection treated for chronic hepatitis C in a large real-world cohort. Our findings suggest that the clinical relevance of HBV-R or HBV-R-related hepatitis after completion of DAA therapy may be negligible.

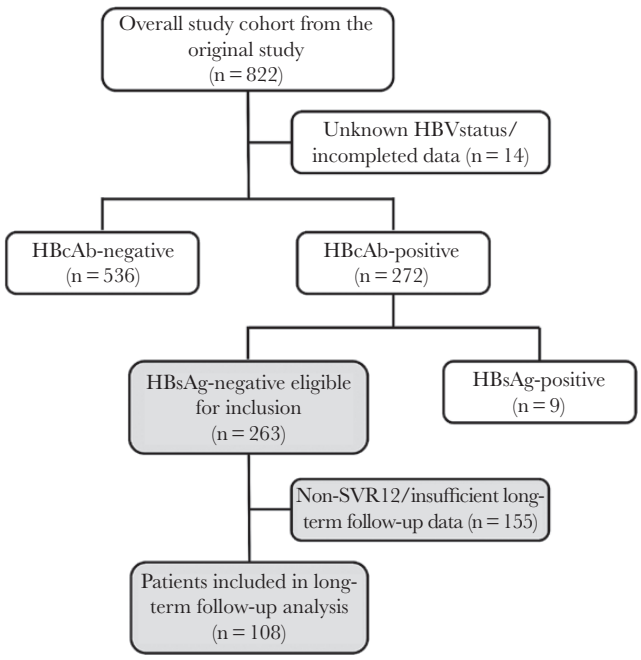

Figure 1. Study cohort overview. Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; SVR, sustained virologic response.

Following the first reports of HBV-R during interferon-free antiviral therapy for chronic HCV, numerous studies have been published investigating the risk of HBV-R in populations with chronic or resolved HBV infection. We were able to show in a systematic review and meta-analysis that the risk of HBV-R in patients with chronic or resolved infection was 24% and 1.4%, respectively [4]. So far, studies have focused on evaluating HBV-R during DAA therapy until 12 weeks thereafter [10, 12–21].

The mechanisms of HBV-R, particularly in patients with resolved HBV infection, are not completely understood. It has been speculated that HBV-R may be associated with the rapid and profound clearance of HCV during DAA therapy, leading to a loss of viral interference mediated by innate or adaptive host immune responses [22, 23].

The topic sparked additional interest when several cases of late HBV-R were reported in patients with resolved infection: Vionett and colleagues reported on a liver transplant recipient with resolved HBV infection who experienced HBV-R 50 weeks after EOT following a 12-week regimen of ledipasvir/sofosbuvir for post-transplant HCV recurrence [8]. In another report, Odolini and colleagues observed HBV-R 4 weeks after EOT in a 72-year old woman with no risk behavior for de novo infection but resolved HBV following sofosbuvir + ribavirin treatment [7]. Earlier, Serper and colleagues investigated hepatic events following DAA therapy in a large US veterans cohort comprising 17 266 HBsAg-negative/HBcAb-positive patients; HBV-R was reported as a possible cause, yet the majority of patients were not systemically tested for HBsAg or HBV DNA [9].

In the present study, we provide for the first time long-term follow-up data (up to 1 year) in 108 patients with resolved HBV infection from a large real-world cohort. However, systematic serologic and molecular testing did not reveal occult or overt HBV-R. A total of 18 patients had increased ALT levels after EOT, but none could be associated with HBV-R.

ALT elevations through SVR12 are not uncommon. Despite HCV clearance, hepatic inflammation may persist in some patients and can be associated with progression of fibrosis. Several risk factors for post-SVR inflammation and/or fibrosis progression, including male gender, daily alcohol consumption, a high body mass index, or presence of nonalcoholic fatty liver disease, have been identified [24, 25]. In our study, patients with ALT elevation had similar risk profiles.

Limitations of our study include the retrospective nature of the analysis. Moreover, follow-up visits beyond SVR12 were performed every 12 weeks only, whereas patients were seen every 4 weeks during DAA therapy. Thus, short-term increases in HBV-DNA levels or reappearance of HBsAg levels cannot be completely ruled out. However, due to sequential testing of HBV DNA or HBsAg levels at EOT, FU12, and the end of

follow-up, up to 1 year after EOT, as well as routine testing of ALT, the risk of missing events of clinically meaningful HBV-R was considered negligible. Finally, the number of patients with complete 1-year follow-up data was relatively low. Moreover, the majority of patients were of Caucasian ethnicity. Thus, data may not be applicable to Asian populations.

Taken together, our results indicate that the risk of HBV-R in DAA-treated patients with resolved HBV infection is low.

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