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Hepatitis B virus reactivation in transplant patients treated for hepatitis C recurrence: Prophylaxis makes the difference

To the Editor:

Hepatitis C virus (HCV) is known to cause suppression of hepatitis B virus (HBV) replication in patients with HBV/HCV coinfection.[1] Loss of HBV suppression following interferon (IFN)-based HCV treatment is a well-known phenomenon[2] and HBV reactivation in patients treated for HCV with direct-acting antivirals (DAAs) has recently attracted clinical attention. Indeed, some of the identified cases had serious outcomes, resulting in liver transplantation or death.[3,4] Subsequent series of HBV/HCV-coinfected patients treated with DAAs have shown that viral reactivation was relatively common in hepatitis B surface antigen (HBsAg)-positive patients, and a meta-analysis identified a similar incidence but an earlier viral reactivation and a higher incidence of hepatitis due to reactivation compared to IFN treatments.[5–9] Liver transplantation (LT) offers a unique model to assess the risk of HBV reactivation associated with DAAs in recipients with HBV markers prior to LT or in recipients of liver donors with HBV markers, given the immunosuppressed state that favours replication, particularly when no HBV prophylaxis is given.

The multicentre prospective cohort CUPILT (ANRS C023 "Compassionate use of Protease Inhibitors in viral C Liver Transplantation"; ClinicalTrials.gov number NCT01944527) enrolled 699 liver recipients between October 2013 and December 2015.[10] Of them, 241 patients with positive pre-transplant HBV markers treated with second generation DAAs for HCV recurrence[10] were included in the present study: at LT, 18 (7.4%) were HBsAg-positive and 223 (92.6%) were HBV core antibody (HBcAb)-positive. The most frequently used DAA combinations were sofosbuvir + NS5A inhibitors (daclatasvir, ledipasvir) ± ribavirin in 87.1% of patients for 12 or 24 weeks, with a rate of sustained virological response at week 12 (SVR12) of 93.4%. HBV DNA and alanine aminotransferase (ALT) levels were obtained at baseline, end of treatment (EOT), and 12 weeks after DAA discontinuation (FU-W12) from medical records or from retrospective testing of available stored plasma samples, using the Abbott RealTime HBV assay. To determine the number of HBV reactivation cases in this population, we included and discussed here all patients with detectable HBV DNA at 1 or more points during HCV treatment follow-up. HBV virological reactivation was defined as a significant increase in HBV DNA levels (>1 $\log_{10}$ IU/ml increase) or levels changing from undetectable (<10 IU/ml) to detectable (>10 IU/ml) after the start of DAAs.[11]

A total of 60 (24.9%) recipients ought to have received HBV prophylaxis, according to international guidelines[12]: *i.e.* HBsAg-positive recipients, recipients of HBcAb-positive donors, and HBcAb-positive human immunodeficiency virus (HIV)-infected patients. However, prophylaxis was recorded in only 48 of these cases (Fig. 1). HBV prophylaxis included hepatitis B immune globulin (HBIG) monotherapy in 6 (12.5%) cases, HBIG + nucleos(t)ide inhibitors in 13 (27.1%), and nucleos(t)ide inhibitors without HBIG in 29 (60.4%). Between transplantation and DAA introduction, the HBV status was reassessed in 193 patients (80.0%), with a mean delay of 21.4 ± 28.5 months (0.0–161.7) before HCV treatment baseline, and 4 (2.1%) were HBsAg-positive.

Overall, 5 (2.1%) had detectable HBV DNA at 1 to 3 time points of DAA treatment follow-up (Fig. 1 and Table 1). Three of these patients were HBsAg-negative and HBcAb-positive at LT with no initial indication of HBV prophylaxis. Patient 0321-048-1 was prospectively determined to be HBV DNA-positive

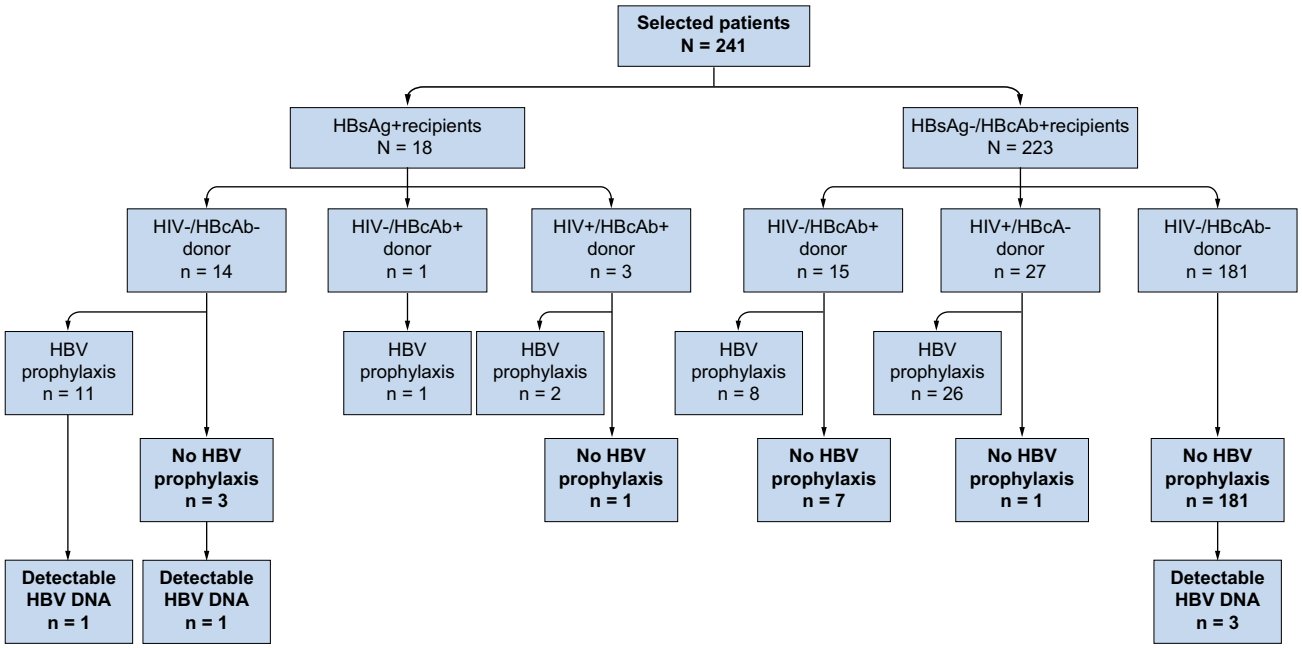

Fig. 1. HBV markers, HBV prophylaxis and detectable HBV DNA during HCV treatment follow-up. HBV, hepatitis B virus; HCV, hepatitis C virus; HBcAb, HBV core antibody; HBsAg, HBV surface antigen; HIV, human immunodeficiency virus.

during DAA therapy, while at DAA introduction a positive HBsAg and a high viral load were demonstrated by the present retrospective study. The liver donor was HBcAb-negative. This *de novo* post-LT-infection was treated with entecavir with an HBV virological response, but a second LT was required due to decompensated cirrhosis. Patient 0327-041-1 had an occult HBV infection with a negative HBsAg, a low-level viremia throughout follow-up without any HBV treatment, and multiple mutations within the S gene (sG112K, sS114P, sT126N, sT127A/T, sY134H, sS136Y, and sS143A). The third patient (0304-009-1) experienced transient very low-level HBV viremia at EOT with further undetectable results and no increase in ALT levels, and was the only 1 of these 3 HBcAb-positive recipients to exhibit an HBV reactivation as defined. Two patients were HBsAg-positive at LT. Patient 0327-021-1 was HBsAg-positive at LT, but HBsAg-negative at DAA baseline, and was no longer receiving HBV prophylaxis. This patient was cirrhotic before starting DAAs, and experienced SVR12. He presented a virological reactivation, as defined, with a low-level viremia detected at FU-W12 and an ALT increase between EOT and FU-W12, and died at FU-W38 from bacterial infection. Patient 0902-013-1 was HBsAg-positive at LT and received tenofovir + HBIG prophylaxis. However, he experienced HBV recurrence with a positive HBsAg before starting DAAs, and a low-level HBV viremia at baseline: HBV treatment adherence was questionable. He exhibited an increased viral load at EOT and developed an oedematous-ascitic decompensation with raised ALT after DAA discontinuation: this patient exhibited the only HBV reactivation with clinical hepatitis in this retrospective study.

The rate of HBV DNA detection was also analysed according to HBV prophylaxis status. Our retrospective study included 193 patients with no HBV prophylaxis: 181 HBcAb-positive recipients with no indication of HBV prophylaxis and 13 patients with an initial indication, but with no prophylaxis recorded before the start of DAA therapy (Fig. 1). Of these 193 patients, 4 had detectable DNA during DAA treatment follow-up, but only 2/4 experienced virological reactivation after starting DAAs. Meanwhile, 48 patients received HBV prophylaxis, and 1/48, with poor prophylaxis adherence, experienced a clinical HBV reactivation.

Thus, among 241 HBV/HCV-coinfected liver transplant recipients treated with DAAs for HCV recurrence, 5 (2.1%) had detectable HBV replication during treatment follow-up, and 3 (1.2%) fulfilled the criteria of virological reactivation, which was clinically significant in a single patient whereas another patient died during the follow-up, from a liver-unrelated cause. The definition of viral reactivation, a >1 $\log_{10}$ IU/ml viral load increase or levels changing from undetectable to detectable after DAA baseline, was quite stringent compared to definitions used in other published studies on this topic: indeed, the consequences of an even minimal replication could be amplified by the immunosuppressive treatment administered after transplantation. Despite this strict definition, only 1.2% experienced viral reactivation, which is quite reassuring. In the liver transplant setting, some specific populations are at high risk of HBV recurrence, such as HBsAg-positive recipients or patients with HBV reactivation; *i.e.*, HBcAb-positive/HIV-positive recipients or recipients of a liver from an HBcAb-positive donor, and HBV prophylaxis is warranted in these cases.[12] In our cohort study, 25% of the patients (60/241) met these conditions, but 12/60 were not provided HBV prophylaxis at DAA start and at least 1 additional patient exhibited poor adherence. Among these 13 patients, 2 viral reactivations with clinical consequences were identified. We hypothesize that the absence of prophylaxis or poor adherence was primarily responsible for the HBV reactivation. Although transplantation is a fertile ground for reactivation due to the immunosuppressive therapy, our results are consistent with previous reports: reactivation during DAA treatment occurs mainly in HBsAg-positive patients, with rates ranging from 2 to 55%.

Meanwhile, 75% of the patients (181/241) were patients with resolved HBV infection at the time of LT (HBsAg-negative/HBcAb-positive), without HIV infection or a liver from an HBcAg-positive donor, who did not require long-term HBV pro-

Table 1. Patients with detectable HBV DNA during HCV treatment follow-up.

No.	HBV status at LT	HIV status	Liver donor HBcAb status	HBV treatment Pre-DAAs	Baseline fibrosis score*	DAA		HBV status at baseline	HBV DNA (log IU/ml)			ALT (IU/ml)			Clinical event
						Regimen	SVR		Baseline	EOT	FU W12	Post-treatment	Baseline	EOT	FU W12	
0321-048-1	HBcAb+	Neg	Neg	None	F4	24-wks SOF + LDV	Yes	HBsAg+	6.64	5.07	1.72		38	16	13	None
0327-041-1	HBcAb+	Neg	Neg	None	F0-F2	12-wks SOF + DCV	Yes	HBcAb+	2.49	2.09	1.3		26	10	13	None
0304-009-1	HBcAb+	Neg	Neg	None	F4	24-wks SOF + DCV	Yes	HBcAb+	Und. <1	1.52	n.a.	Und. <1 (W48)	72	15	16	None
0327-021-1	HBsAg+	Neg	Neg	None	F4	12-wks SOF + DCV	n.a.	HBcAb+	Und. <1	Und. <1	2.17	n.a.	37	16	30	Death at FU-W38
0902-013-1	HBsAg+	Neg	Neg	TDF + HBIG	F4	24-wks SOF + DCV	Yes	HBsAg+	1.49	3.46	Und. <1		19	n.a.	142	Ascites

DCV, daclatasvir; HBIG, hepatitis B immune globulin; HBV, hepatitis B virus; HCV, hepatitis C virus; n.a., not available; RBV, ribavirin; SOF, sofosbuvir; TDF, tenofovir disoproxil fumarate.
* Metavir score.

phylaxis. An increased reactivation risk could have been expected for this specific population. In our cohort, 3 (1.7%) of these patients had detectable HBV DNA during DAA treatment follow-up, but only 1 HBV reactivation fulfilled the definition of HBV reactivation without any clinical consequences.

Our study has some limitations, including the observational design of the CUPILT cohort, the absence of a control transplant population with HBV mono-infection, and the lack of routine serological HBV testing at the start of DAAs in 20% of patients. However, in this transplant setting HBV status at the time of LT is relevant to assess the risk of HBV reactivation.

In conclusion, our study highlights the need to assess HBV markers at HCV treatment baseline, as recommended by recent guidelines,[13] and as stressed by Bersoff-Matcha *et al.* who showed that not of all the cases submitted to the FAERS had an HBsAg test result reported.[4] According to current guidelines, all patients starting therapy with HCV DAAs must be assessed before treatment initiation for HBsAg, HBsAb, and HBcAb status, and patients at risk of HBV reactivation (both HBsAg and anti-HBc-positive patients) should have their HBV DNA levels monitored at baseline, during DAA therapy and for several weeks after stopping treatment. This monitoring during DAA follow-up is crucial to a timely implementation of HBV prophylaxis, if required. However, our study is very reassuring and allows us to conclude that if a risk exists, it is extremely rare. We have identified a single reactivation event exclusively attributable to DAAs and furthermore without clinical impact. Our retrospective study also identified an occult HBV infection which did not lead to reactivation, suggesting that factors other than detectable HBV DNA at baseline may influence HBV reactivation upon treatment with DAAs. Additional studies may be necessary to determine the risk factors for HBV reactivation, but our study confirms that its occurrence is very rare among HBsAg-negative anti-HBc-positive patients, including in the liver transplant setting. Our results reaffirm that, beyond the risk of HBV reactivation, this subgroup of patients should undergo clinical monitoring for liver events as recommended by the liver transplant guidelines. However, a specific monitoring during DAA treatment seems dispensable.

Thus, HBV reactivation in the setting of LT is potentially preventable. Regardless of HBV-HCV coinfection and LT, proper screening of HBV status is necessary and essential. It is important to recognize that our study has shown that guidelines on prophylaxis and monitoring in transplant patients were not rigorously followed in "real life", but that this ultimately had little clinical impact.

Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.02.019.

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