SAT-154

Association of Post-treatment Virologic Relapse and Biochemical Flares With HBV Serum Biomarkers in Long-term Virologically Suppressed HBeAg negative Patients Stopping NA Treatment: Exploratory Analyses From the Control Arm of the REEF-2 Study

Florian van Bömmel,[1,*] Thierry Verbinnen,[2] Kosh Agarwal,[3] Thomas Vanwolleghem,[4] Pietro Lampertico,[5,6] Maria Buti,[7] Ewa Janczewska,[8] Marc Bourliere,[9] John Jezorwski,[10] Kathleen Donohue,[11] Gloria Kim,[12] Thomas N. Kakuda,[13] Sandra De Meyer,[2] Adam Bakala,[2] Oliver Lenz,[2] Michael Biermer[2]

[1]Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany; [2]Janssen Pharmaceutica NV, Beerse, Belgium; [3]Institute of Liver Studies, King's College Hospital, Denmark Hill, London, UK; [4]University of Antwerp, Faculty of Medicine & Health Sciences, Laboratory of Experimental Medicine & Pediatrics, Viral Hepatitis Research Group, Antwerp, Belgium; [5]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy; [6]CRC "A. M. and A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [7]Hospital General Universitari Vall Hebron and CIBER EHD del Instituto Carlos III, Barcelona, Spain; [8]Medical University of Silesia in Katowice, Faculty of Public Health in Bytom, Bytom, Poland; [9]Hôpital Saint-Joseph, Department of Hepatology and Gastroenterology, Marseille, France; [10]Janssen Research & Development, LLC, Titusville, NJ, USA; [11]Cytel Inc., Waltham, MA, USA; [12]IQVIA, Durham, NC, USA; [13]Janssen Research & Development, LLC, Brisbane, CA, USA.

*Presenting author.

Introduction

- The phase 2b REEF-2 study (ClinicalTrials.gov Identifier: NCT04129554) assessed the efficacy and safety of the combination of short-interfering RNA JNJ-73763989 (JNJ-3989), capsid assembly modulator JNJ-56136379 (JNJ-6379; bersacapavir), and nucleos(t)ide analogue (NA) compared to NA only in long-term, virologically suppressed hepatitis B e antigen (HBeAg) negative patients with chronic hepatitis B (CHB)[1]
  - All treatments were discontinued in both arms at Week 48, followed by 48 weeks of follow-up[1]
  - In the NA arm, a higher rate of virologic relapse, post-treatment alanine aminotransferase (ALT) flares, and NA retreatment with a lower rate of sustained off-treatment hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA suppression were observed compared to the JNJ-3989 arm[1]
- While several recent studies have demonstrated that stopping NA treatment can result in HBsAg seroclearance in some patients with CHB,[2,3] almost all patients who stop NA treatment experience an off-treatment transient virologic relapse, which can be associated with severe ALT increases in some patients
- Varying levels of end of treatment (EOT) viral parameters, such as HBsAg, hepatitis B core-related antigen (HBcrAg), HBV RNA, and hepatitis B core antibody (anti-HBc), have been demonstrated to be associated with the risk of virologic relapse and biochemical (ALT) flares after stopping NA treatment[4–8]

Objective

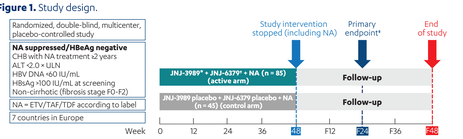
- To characterize post-treatment virologic relapses and biochemical flares in the NA arm of the REEF-2 study and assess their association with EOT HBV serum markers

Methods

Study Design

- The current analysis assessed the post-treatment responses of patients in the NA (control) arm of the REEF-2 study (**Figure 1**)

Figure 1. Study design.



ETV, entecavir; F, follow-up; LLOQ, lower limit of quantification; PO, oral; SC, subcutaneous; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil; ULN, upper limit of normal. *200 mg SC every 4 weeks. †250 mg PO daily. ‡HBsAg seroclearance (HBsAg <LLOQ [0.05 IU/mL]) at Week 72 without restarting NA treatment.

NA Retreatment Criteria

- Patients needed to restart NA treatment immediately in the case of signs of decreasing liver function or (after protocol amendment) HBV DNA >100,000 IU/mL (irrespective of confirmation and/or ALT increase)
- Restart of NA was to be considered in the case of post-treatment HBeAg seroreversion, confirmed (≥4 weeks apart) post-treatment increases in HBV DNA >20,000 IU/mL, or HBV DNA >2,000 IU/mL in combination with ALT >5 × ULN

Definitions

- Virologic relapse was defined as confirmed (ie, 2 consecutive visits) HBV DNA >2,000 IU/mL off treatment
- Biochemical flare was defined as confirmed ALT and/or aspartate transaminase (AST) ≥3 × ULN and ≥3 × nadir off treatment

Assays

- Baseline and post-baseline ALT, HBV DNA, HBeAg, and HBsAg levels were assessed at a central laboratory (Labcorp) during the conduct of this study using "standard" assays. "Standard" HBV RNA levels were assessed at DDL Diagnostic Laboratory (The Netherlands) using a validated quantitative reverse transcriptase-polymerase chain reaction with a limit of detection (LOD) of 310 copies/mL.[9] "Standard" HBcrAg levels were determined at Labcorp using the Lumipulse® platform (Fujirebio) with an LLOQ of 3.0 $\log_{10}$ U/mL
- Exploratory analyses of the selected set of samples were performed post hoc and included reanalysis of serum HBcrAg and HBV RNA levels and analysis of anti-HBc immunoglobulin G (IgG)
  - HBcrAg was reanalyzed at DDL Diagnostic Laboratory using the same "standard" assay (Fujirebio). In contrast to the reporting by the central laboratory, HBcrAg values <LLOQ of 3.0 $\log_{10}$ U/mL were considered. Samples with an HBcrAg result <2.6 $\log_{10}$ U/mL were categorized as <LLOQ target not detected (TND), and samples with an HBcrAg result ≥2.6 to <3.0 $\log_{10}$ U/mL were categorized as <LLOQ target detected
  - Exploratory HBV RNA analysis was performed at bioMONTR® (United States) using the Abbott HBV RNA assay.[10] This assay is available in 2 versions according to the sample input volume being either 0.2 mL (LLOQ of 22 copies/mL) or 0.6 mL (LLOQ of 11 copies/mL)
  - Anti-HBc IgG levels were analyzed at DDL Diagnostic Laboratory using the Lumipulse® (Fujirebio) anti-HBc assay[11]

Results

Patients

- 41/45 patients enrolled in the REEF-2 NA control arm were included in this analysis (2 patients discontinued study treatment at Week 2 and did not enter follow-up, 1 patient discontinued study treatment at Week 8 and entered follow-up but continued NA treatment, and 1 patient completed study treatment but did not enter follow-up)
- All patients were long-term virologically suppressed (≥2 years) and HBeAg negative at screening. The majority were male (64%); the mean age was 47.4 years; and, while the study was based in Europe, ~18% of patients were Asian. The mean duration of NA treatment at study entry was 8.1 (range: 2.2-17.4) years

Exploratory Assay Analyses

HBV RNA

- EOT "standard" assay HBV RNA data were available for 40/41 patients, and 39/40 (97.5%) had HBV RNA <LOD of the "standard" assay (LOD = 310 copies/mL[9]) at EOT (**Table 1**)
- All EOT samples (N = 41) were reanalyzed with the Abbott HBV RNA assay:
  - 23 samples were reanalyzed using a sample input volume of 0.6 mL. The other 18 samples were reanalyzed using a sample input volume of 0.2 mL due to limited available sample volume
  - After reanalysis with the Abbott HBV RNA assay, 6/41 (15%) patients had HBV RNA <LLOQ TND at EOT; 5/18 (28%) and 1/23 (4%) patients were analyzed using sample input volumes of 0.2 and 0.6 mL, respectively (**Table 1**)

HBcrAg

- "Standard" testing at the central laboratory showed that 24/41 (58.5%) patients had HBcrAg <LLOQ (ie, <3.0 $\log_{10}$ U/mL) at EOT (**Table 1**)
- For exploratory retesting, all EOT samples with a result of HBcrAg <3.0 $\log_{10}$ U/mL were considered:
  - All 24 reanalyzed samples were confirmed to have HBcrAg <3.0 $\log_{10}$ U/mL in the reanalysis, and 20 samples were determined to have HBcrAg <2.6 $\log_{10}$ U/mL (ie, <LLOQ TND; **Table 1**)

Anti-HBc IgG

- The mean (range) anti-HBc IgG level at EOT was 1,366 (7-11,000) IU/mL, and 23/41 (56%) patients had EOT anti-HBc IgG levels <300 IU/mL (**Table 1**)

Table 1. REEF-2 NA Control Arm Patient Disease Characteristics at EOT

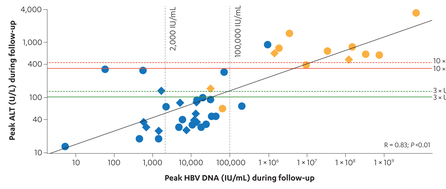
"Standard" assay*†		Exploratory analysis/assay*†		
HBeAg negative	41 (100)	–		
Mean (range) HBsAg, $\log_{10}$ IU/mL	3.42 (1.8-4.7)	–		
HBsAg <1,000 IU/mL	13 (31.7)*	–		
HBV DNA <LLOQ‡	41 (100)	–		
HBcrAg <LLOQ‡	24 (58.5)	HBcrAg <2.6 $\log_{10}$ U/mL (ie, <LLOQ TND)		20 (48.8)
		HBcrAg ≥2.6 to <3.0 $\log_{10}$ U/mL (<LLOQ target detected)		4 (9.8)
HBV RNA <LOD¶ (n = 40)	39 (97.5)*	HBV RNA assay,** 0.2 mL	≥LLOQ	11 (26.8)
			<LLOQ target detected	2 (4.9)
			<LLOQ TND	5 (12.2)
		HBV RNA assay,** 0.6 mL	≥LLOQ	22 (53.6)
			<LLOQ target detected	0
			<LLOQ TND	1 (2.4)
ALT <1 × ULN	38 (92.7)	–		
–		Mean (range) anti-HBc IgG, IU/mL		1,367 (7-11,000)

"Standard" assays were run at central laboratories during the study; exploratory assays and analyses were performed post hoc on the selected set of samples. *Values are n (%) unless otherwise noted. †The denominator is the overall population (N = 41). ‡1 patient had HBsAg >100 IU/mL at EOT. §HBV DNA LLOQ = 15 IU/mL. ‖HBcrAg LLOQ = 3.0 $\log_{10}$ U/mL. ¶HBV RNA LOD = 310 copies/mL. **The 1 patient with HBV RNA >LOD in the "standard" assay also had detectable and quantifiable HBV RNA in the exploratory assay. ††HBV RNA 0.2 mL (n = 18) and 0.6 mL (n = 23) sample input assay LLOQ = 22 and 11 copies/mL, respectively.

Relationship Between Peak HBV DNA Levels During Virologic Relapse and Magnitude of Off-treatment Biochemical Flares

- Peak HBV DNA levels during virologic relapse were associated with the magnitude of off-treatment ALT flares (R = 0.83; *P* <0.01; **Figure 2**)
- 10/11 (91%) patients with virologic relapse and confirmed peak HBV DNA >100,000 IU/mL had peak ALT levels ≥10 × ULN
  - The 1 patient who did not have ALT ≥10 × ULN had a peak ALT level ~9 × ULN
  - 1 other patient had virologic relapse but with an unconfirmed (ie, at a single time point) peak HBV DNA value >100,000 IU/mL. This (male) patient had only limited elevation of ALT levels (peak ALT of 70 U/L)
- None of the 16 patients with virologic relapse and confirmed peak HBV DNA levels >2,000 to <100,000 IU/mL had peak ALT levels ≥10 × ULN
- 3 patients had off-treatment ALT flares (2 males with peak ALT ~7 × ULN and 1 female with peak ALT ~4 × ULN) without virologic relapse (peak HBV DNA levels of 54, 532, and 1,620 IU/mL, respectively)

Figure 2. Relationship between peak HBV DNA levels and peak ALT levels during follow-up.



Diamonds and circles represent data for female and male patients, respectively. Data in yellow indicate patients who restarted NA treatment. Solid and dashed horizontal lines represent ALT values of 3 × ULN (green) and 10 × ULN (red) for females (102 and 340 U/mL) and males (129 and 430 U/L), respectively. The solid black line is a linear regression trend line.

Kinetics of Other Viral Markers During Virologic Relapse

- Virologic relapse was generally associated with parallel increases in other viral markers, especially among patients with high peak HBV DNA levels during follow-up (**Figure 3**)
- Among patients with **virologic relapse and confirmed peak HBV DNA levels >100,000 IU/mL** (n = 11), during virologic relapse:
  - 11 (100%) had confirmed HBV RNA increases ≥2 $\log_{10}$ cp/mL from EOT levels (all had HBV RNA <LOD of "standard" assay at EOT)
  - 11 (100%) had >1.0 $\log_{10}$ IU/mL increase in anti-HBc IgG levels from EOT
  - 8 (73%) had confirmed HBcrAg increase ≥1.0 $\log_{10}$ U/mL from EOT levels (including 4 patients who had EOT HBcrAg levels <LLOQ)
  - 8 (73%) had transient HBsAg increase ≥0.5 $\log_{10}$ IU/mL from EOT levels (5 had ≥1 $\log_{10}$ IU/mL increase)
  - 4 (36%) had transient detectable HBeAg levels during follow-up (maximum increases in HBeAg levels ranged from 0.5 to 3.9 $\log_{10}$ IU/mL)
  - 10 (91%) restarted NA treatment, which resulted in declines in virologic markers in all patients
    - 7 and 8 had HBV DNA <LLOQ and ALT normalization (<ULN) at Follow-up Week 48, respectively
- Among patients with **virologic relapse and confirmed peak HBV DNA levels >2,000 to ≤100,000 IU/mL** (n = 16), during off-treatment follow-up:
  - Increases in HBV RNA and HBcrAg levels were more modest, less frequent, and, in the majority of patients, at single time points (ie, blips)
  - No associated increases in HBsAg levels and no transient detectable HBeAg levels were observed
  - 2 (13%) restarted NA treatment and had HBV DNA <LLOQ at Follow-up Week 48
  - All 14 others who were not retreated with NA still had detectable HBV DNA levels at Follow-up Week 48 (8 with HBV DNA levels ≥2,000 IU/mL)
- Among patients with **no virologic relapse** (n = 14), during off-treatment follow-up:
  - 7 (50%) had detectable off-treatment HBV DNA levels varying between >200 and ≤2,000 IU/mL. 5 (36%) additional patients had detectable off-treatment HBV DNA >200 IU/mL with single peak values >2,000 IU/mL (n = 4) and >20,000 IU/mL (n = 1)
  - Few had detectable HBV RNA and HBcrAg levels, mostly at single time points
  - 1 (7%) had transiently detectable HBeAg, and none had increases in HBsAg
  - None were retreated with NA, and 12 (86%) had HBV DNA >LLOQ and <2,000 IU/mL, and 2 had HBV DNA <LLOQ at Follow-up Week 48

Association of Post-treatment Virologic Relapse and Biochemical Flares With EOT HBV Serum Biomarkers

HBV RNA, HBcrAg, HBsAg, and HBV DNA

- A similar proportion of patients with HBV RNA detectable and TND at EOT had virologic relapse or biochemical flares (**Table 2**)
- A higher frequency of virologic relapse with peak HBV DNA >100,000 IU/mL and biochemical flares with peak ALT ≥10 × ULN was observed in patients with detectable HBcrAg at EOT compared to those with HBcrAg TND (**Table 2**)
- A higher frequency of virologic relapse with peak HBV DNA >100,000 IU/mL and biochemical flares was observed in patients with HBsAg <1,000 IU/mL at EOT compared to those with HBsAg ≥1,000 IU/mL (**Table 2**)
- A similar proportion of patients with HBV DNA <LLOQ detectable and TND at EOT had virologic relapse or biochemical flare (data not shown)

Anti-HBc IgG

- Patients with anti-HBc IgG titers <300 IU/mL at EOT had a significantly higher frequency of virologic relapse with peak HBV DNA >100,000 IU/mL or biochemical flares than patients with EOT anti-HBc IgG titers ≥300 IU/mL (**Table 2**; **Figure 4**). Notably, none of the 11 patients with anti-HBc IgG titers ≥300 IU/mL at EOT had peak HBV DNA >100,000 IU/mL or peak ALT ≥10 × ULN (**Table 2**; **Figure 4**)
- For prediction of (a) the absence of severe biochemical flare (ie, peak ALT level ≥10 × ULN) and (b) the absence of virologic relapse with peak HBV DNA >100,000 IU/mL, patients with EOT anti-HBc IgG ≥300 IU/mL had:
  - (a) 58% sensitivity, 100% specificity; positive predictive value (PPV) of 100%, negative predictive value (NPV) of 43%
  - (b) 60% sensitivity, 100% specificity; PPV of 100%, NPV of 48% (**Figure 5**)
- With the addition of HBcrAg, the accuracy measurements improved compared to the model with anti-HBc IgG alone. Using an example for the Firth's logistic regression, a patient with anti-HBc IgG ≥300 IU/mL and HBcrAg TND at EOT had a predicted probability of 0.009 to have a peak ALT level ≥10 × ULN and 0.01497 to have peak HBV DNA >100,000 IU/mL (vs 0.026 with anti-HBc IgG alone; **Figure 5**)

Univariate and Multivariate Logistic Regression of EOT Virologic Parameters

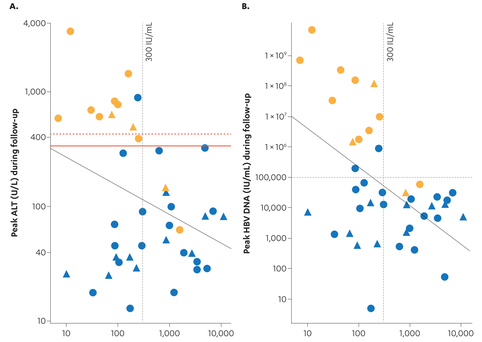
- EOT HBsAg, HBcrAg, and anti-HBc IgG each showed univariate association with the outcome variable absence of peak ALT ≥10 × ULN during follow-up (**Table 3**)
- HBsAg was no longer significant when adjusting for HBcrAg and anti-HBc IgG in a multivariate model. When adjusting for anti-HBc IgG, HBcrAg was marginally significant (**Table 3**). The odds ratio (OR) for not having a peak ALT level ≥10 × ULN for those with EOT anti-HBc IgG <300 IU/mL was 21.402 (95% confidence interval [CI], 2.187-2,902.034; *P* = 0.0457). For those with EOT HBcrAg <LLOQ TND, the OR was 7.150 (95% CI, 1.161-80.166; *P* = 0.0564)

Table 2. Proportion of REEF-2 NA Control Arm Patients With Post-treatment Virologic Relapse and Biochemical Flare by EOT Virologic Parameters

EOT variables/type of NA	N	Virologic relapse (confirmed HBV DNA >2,000 IU/mL		Biochemical flare (ALT ≥3 × ULN)	
		Any virologic flare	Peak HBV DNA >100,000 IU/mL	Any ALT flare	Peak ALT ≥10 × ULN
Patients with EOT data who entered follow-up, n (%)	41	27 (65.9)	11 (26.8)	16 (39.0)	10 (24.4)
HBV RNA					
Detectable*	35	23 (65.7)	9 (25.7)	13 (37.1)	9 (25.7)
TND*	6	4 (66.7)	2 (33.3)	3 (50.0)	1 (16.7)
P value*		1.0000	0.6514	0.6624	1.0000
HBcrAg					
Detectable*	21	17 (81.0)	**9 (42.9)**	10 (47.6)	**9 (42.9)**
TND*	20	10 (50.0)	**2 (10.0)**	6 (30.0)	**1 (5.0)**
P value*		0.0516	**0.0325**	0.3408	**0.0089**
Anti-HBc IgG					
<300 IU/mL	23	16 (69.6)	**11 (47.8)**	12 (52.2)	**10 (43.5)**
≥300 IU/mL	11	11 (61.1)	**0**	4 (22.2)	**0**
P value*		0.7417	**0.0008**	0.0626	**0.0021**
HBsAg					
<1,000 IU/mL‖	13	9 (69.2)	6 (46.2)	8 (61.5)	**6 (46.2)**
≥1,000 IU/mL	28	18 (64.3)	5 (17.9)	8 (28.6)	**4 (14.3)**
P value*		1.0000	0.0727	0.0835	**0.0485**

Bold values are significant. *†LLOQ detectable or <LLOQ. ‡LLOQ, 12-sided *P* value from Fisher's exact test. No adjustments for multiplicity were performed. Statistical testing was performed to compare the exploratory biomarker classifications among the patients who had any virologic flare (yes vs no), off-treatment virologic flare of >100,000 IU/mL (yes vs no), any ALT flare (yes vs no), and peak ALT ≥10 × ULN in the follow-up phase (yes vs no). ‖Includes 1 patient with EOT HBsAg >100 IU/mL.

Figure 4. (A) Peak ALT and (B) peak HBV DNA during follow-up versus EOT anti-HBc IgG levels.



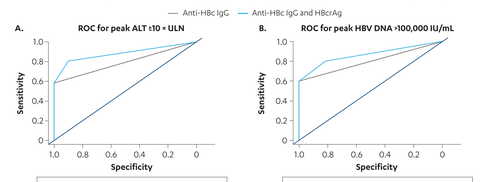
Circles and triangles represent data for male and female patients, respectively. Data in yellow indicate patients who restarted NA treatment. Solid and dashed horizontal red lines in panel A represent ALT values of 10 × ULN for females (340 U/L) and males (430 U/L), respectively. The solid black lines are linear regression trend lines.

Table 3. Logistic Regression Model for Not Having a Biochemical Flare With Peak ALT ≥10 × ULN During Follow-up by EOT Virologic Parameters

EOT variables	Univariate model		Multivariate model	
	OR (95% CI)*	*P* value	OR (95% CI)*	*P* value
HBV DNA	1.381 (0.043-97.797)	0.8640	–	–
HBV RNA <LLOQ TND	1.731 (0.235-35.495)	0.6368	–	–
HBcrAg <LLOQ TND	14.248 (2.261-280.182)	**0.0174**	7.150 (1.161-80.166)	0.0564
Anti-HBc IgG ≤300 IU/mL†	28.775 (3.204-3,820.88‡)	**0.0282**	21.402 (2.187-2,902.034‡)	**0.0457**
HBsAg <1,000 IU/mL	0.194 (0.039-0.862)	**0.0347**	–	–

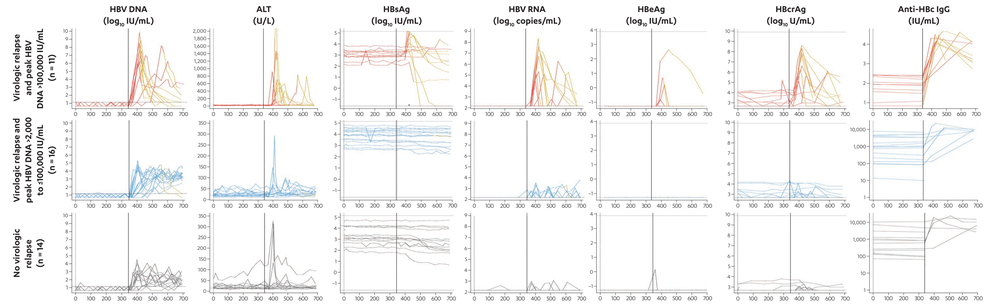
Bold values are significant. *Profile likelihood method. †Logistic regression using Firth's bias correction. ‡The R software package calculated the upper CIs to be 3,820.88 and 2,902.034.

Figure 5. Sensitivity and specificity of anti-HBc IgG and HBcrAg for predicting (A) the absence of biochemical flare with peak ALT ≥10 × ULN and (B) virologic relapse with peak HBV DNA >100,000 IU/mL.



AUC, area under the curve; ROC, receiver operating characteristic.

Figure 3. Individual HBV DNA, ALT, HBsAg, HBV RNA, HBeAg, HBcrAg, and anti-HBc profiles by peak HBV DNA value during follow-up.



The color of the lines indicates the level of virologic relapse for individual patients. Red: HBV DNA >100,000 IU/mL; blue: >2,000 to ≤100,000 IU/mL; gray: no virologic relapse. Time points shown in yellow indicate time points after the start of NA retreatment. Data shown are from "standard" assays. X-axis values represent days after the start of study treatment. Vertical lines indicate EOT (Week 48). Virologic relapse is defined as confirmed off-treatment HBV DNA levels >2,000 IU/mL. *1 patient experienced severe HBV reactivation with subacute liver failure that led to transplantation at Follow-up Week 13.

Key Findings

- In the NA only arm, off-treatment virologic relapses and ALT flares were experienced by 27 (66%) and 16 (39%) patients, respectively, after NA treatment discontinuation
- Peak HBV DNA levels during virologic relapse were associated with the magnitude of ALT flares
- Assessment of EOT viral markers and off-treatment response showed:
  - Virologic relapse and ALT flares were observed at a similar rate for patients regardless of the detectability of HBV RNA
  - Virologic relapse and biochemical flares with high peak HBV DNA or ALT values were more frequent in patients with detectable HBcrAg and HBsAg <1,000 IU/mL at EOT
  - None of the 18 patients with anti-HBc IgG ≥300 IU/mL at EOT had peak HBV DNA >100,000 IU/mL or peak ALT ≥10 × ULN

Conclusions

- In patients discontinuing NA treatment, the increases in HBV DNA during virologic relapse correlated with peak levels of ALT
- EOT anti-HBc IgG levels ≥300 IU/mL were strongly associated with the absence of high peak HBV DNA virologic relapse (>100,000 IU/mL) and high peak ALT flares (≥10 × ULN); this association was weaker for EOT HBcrAg and HBsAg levels and absent for HBV RNA

References

1. Agarwal K, et al. Presented at: AASLD The Liver Meeting; November 4–8, 2022; Washington, DC, USA.
2. Berg T, et al. *J Hepatol*. 2017;67(5):918-924.
3. van Bömmel F, et al. *J Hepatol*. 2023;78(5):926-936.
4. Fan R, et al. *Clin Gastroenterol Hepatol*. 2020;18(3):719-727.e7.
5. Ohlendorf V, et al. *Liver Int*. 2022;42(12):2674-2682.
6. Chi H, et al. *Clin Gastroenterol Hepatol*. 2019;17(1):182-191.e1.
7. Adrareda C, et al. *J Hepatol*. 2023;78(4):731-741.
8. Liu J, et al. *Hepatology*. 2019;70(3):1045-1055.
9. van Bömmel F, et al. *Hepatology*. 2015;61(1):66-76.
10. Anderson M, et al. *Hepatol Commun*. 2023;7(9):e0099.
11. Cavigila GP, et al. *Diagn Microbiol Infect Dis*. 2020;96(4):114985.

Acknowledgments

This study was supported by Janssen Research & Development, LLC. Editorial support was provided by Kim Caldwell, PhD, of Lumanity Communications Inc., and was funded by Janssen Global Services, LLC.

Disclosures

Full consults for, is on the speakers bureau for, and received grants from Gilead, Bristol Myers Squibb, and Roche; and has scientific collaboration with Roche and Janssen. T Verbinnen, JJ, TNK, SDM, AB, OL, and M Biermer are employees of Janssen and may hold stock in Johnson & Johnson. KA served on the advisory board/speakers bureau for Arbutus, Assembly, Allgos, Biotest, Bluejay, Drug Farm, GSK, Gilead, Janssen, Intercept, Merck, Roche, Sagimet, Sobi, and Vaccitech; and received research support from Gilead and Abbott. T Vanwolleghem receives grants from Gilead and Bristol Myers Squibb; and serves as a consultant for Janssen, Gilead, and AbbVie. PL serves on the advisory board/speakers bureau for Bristol Myers Squibb, Roche, Gilead, GSK, AbbVie, MSD, Arrowhead, Alnylam, Janssen, Spring Bank, WIYK, Eiger BioPharmaceuticals, Antios Therapeutics, Aligos, and Vir Biotechnology. M Buti received grants from Gilead; and gave sponsored lectures for Gilead and AbbVie. EJ receives fees for clinical trials from Janssen-Cilag, GSK, Immunocore, Bristol Myers Squibb, Novo Nordisk, Inventiva, Cymabay, Dr. Falk, Grifols, Cellaion, MSD, Exelixis, Callidtas, Sagimet, and Axcella; and serves on advisory boards for Novo Nordisk and Cellaion. M Bourliere served as a consultant for AbbVie, Gilead, Intercept, and Roche; gave sponsored lectures for Gilead, AbbVie, Roche, and Intercept; and received grants from Gilead and AbbVie. KD is an employee of Cytel. GK is an employee of IQVIA.

Presented at the European Association for the Study of the Liver (EASL) International Liver Congress™; June 21-24, 2023; Vienna, Austria.