Baseline Characteristics of Hepatitis Delta Patients Enrolled Across Phase 2 and 3 Studies of Bulevirtide

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Key Findings

- **Higher baseline ALT levels in patients with CHD are associated with male sex, higher LSM, and HDV RNA levels; no association was found with BMI, concomitant nucleos(t)ide therapy, or presence of cirrhosis**
- **Higher baseline levels of HDV RNA are associated with younger age, HBeAg-positive status, and higher levels of ALT and HBsAg**
- **The small subset of HBeAg-positive patients with CHD tended to present with elevated HBV DNA, HDV RNA, and HBsAg levels but not higher ALT levels; such patients were more likely to be receiving concomitant nucleos(t)ide therapy**

Conclusions

Based on a large cohort of 532 untreated HDV patients, males and those with higher HDV viral load may be at risk of greater biochemical disease activity regardless of BMI, nucleos(t)ide therapy, or the presence of cirrhosis

HBeAg-positive patients with CHD may represent a distinct subset of CHD in which the association between higher HDV viral load and greater biochemical disease activity is less straightforward

References: 1. Stockdale AJ, et al. *J Hepatol*. 2020;73:523-32. **2.** Da B, et al. *Gastroenterol Rep*. 2019;7:231-45. **3.** Soo A, et al. EASL 2023 Poster WED-158.

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Introduction

- Chronic hepatitis delta (CHD) represents the most severe form of chronic viral hepatitis and is estimated to affect between 10 and 20 million worldwide[1]
- Patients with CHD often present with elevated alanine aminotransferase (ALT) levels indicative of ongoing intrahepatic necroinflammation, with ranges of ALT that can be quite wide[2]
- The clinical phenotype of patients with CHD and higher ALT levels compared with the general population of people with CHD is unknown
- Previous analysis of data from 3 trials of bulevirtide (BLV; N = 414) revealed a weak correlation between levels of hepatitis delta virus (HDV) RNA and ALT in untreated CHD patients[3]

Objective

- This analysis aimed to detail the demographic and clinical characteristics of patients with CHD who participated in 4 BLV clinical trials and identify the phenotype of untreated CHD patients with higher biochemical disease activity

Methods

- Cross-sectional analysis using pooled baseline data from 532 patients with CHD enrolled in 4 BLV trials: the MYR202 (Phase 2; NCT03546621), MYR203 (Phase 2; NCT02888106), MYR204 (Phase 2; NCT03852433), and MYR301 (Phase 3; NCT03852719) studies
- Key inclusion criteria: HDV RNA positive at screening, without cirrhosis or with compensated cirrhosis determined by the investigator, and elevated ALT (≥ upper limit of normal [ULN] to <10 × ULN)
  - ALT ULN: ≤31 U/L for females and ≤41 U/L for males (Russian sites); ≤34 U/L for females and ≤49 U/L for males (all other sites)
- Key exclusion criteria: Child-Pugh-Turcotte score B or C, current or prior hepatic decompensation (history of or within the last 2 years, depending on study), and total bilirubin ≥34.2 µmol/L
- Patients were categorized into groups (terciles) based on ALT and HDV RNA values and by hepatitis B e antigen (HBeAg) status
- Fisher's exact test and ANOVA were used for comparison among groups for categorical variables and continuous variables, respectively
  - ALT: <69 U/L; ≥69 to ≤112 U/L; >112 U/L
  - HDV RNA: <4.93 $\log_{10}$ IU/mL; ≥4.93 $\log_{10}$ IU/mL to ≤6.04 $\log_{10}$ IU/mL; >6.04 $\log_{10}$ IU/mL

Results

Table 1. Demographic and Baseline Disease Characteristics by Baseline ALT Tercile

	Total Cohort (N = 532)	ALT <69 U/L (n = 175)	ALT ≥69 to ≤112 U/L (n = 180)	ALT >112 U/L (n = 177)	*P* value
Age, years, mean (SD)	40 (9)	41 (9)	39 (9)	41 (9)	.3246
Male sex, n (%)	**346 (65)**	**91 (52)**	**123 (68)**	**132 (75)**	**<.0001**
Race, n (%)					.6282
Asian	58 (11)	20 (11)	17 (9)	21 (12)	
Black or African descent	9 (2)	1 (1)	4 (2)	4 (2)	
White	464 (87)	153 (87)	159 (88)	152 (86)	
BMI, kg/m^2, mean (SD)	25.1 (3.8)	24.7 (3.8)	25.1 (3.7)	25.5 (3.9)	.1455
BMI ≥30 kg/m^2, n (%)	52 (10)	15 (9)	17 (9)	20 (11)	.6812
ALT, U/L, median (Q1, Q3)	**87 (60, 131)**	**52 (43, 59)**	**87 (76, 98)**	**165 (131, 231)**	**<.0001**
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	**5.3 (1.3)**	**4.9 (1.5)**	**5.4 (1.3)**	**5.5 (1.1)**	**<.0001**
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	1.3 (1.4)	1.4 (1.5)	1.2 (1.3)	1.2 (1.4)	.3983
HBsAg, $\log_{10}$ IU/mL, mean (SD)	**3.8 (0.6)**	**3.9 (0.6)**	**3.9 (0.6)**	**3.7 (0.6)**	**.0008**
HBeAg positive, n (%)	54 (10)	24 (14)	15 (8)	15 (8)	.1797
Nucleos(t)ide therapy,[a] n (%)	178 (33)	57 (33)	58 (32)	63 (36)	.7626
Prior interferon exposure, n (%)	244 (46)	79 (45)	73 (41)	92 (52)	.0924
LSM, kPa, mean (SD)	**13.8 (8.1)**	**12.4 (6.9)**	**13.2 (7.9)**	**15.9 (8.8)**	**.0003**
Cirrhosis present, n (%)	203 (38)	65 (37)	66 (37)	72 (41)	.9599

P values for comparison among ALT terciles used Fisher's exact test or ANOVA. [a]Defined as being on nucleos(t)ide therapy at baseline. HDV GT-1 was the most common (n = 501, 94%) followed by HDV GT-2 (n = 5, 1%), HDV GT-5 (n = 5, 1%), and HDV GT-6 (n = 1, 0%); missing (n = 19). HBV genotype, n (%): genotype A, 36 (7); genotype C, 1 (0); genotype D, 296 (56); genotype E, 3 (1); genotype H, 1 (0); missing, 195 (37). ALT, alanine aminotransferase; ANOVA, analysis of variance; BMI, body mass index; GT, genotype; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; LSM, liver stiffness measurements; Q, quartile.

- The CHD population enrolled in the BLV trials was predominantly male and White, with HDV genotype 1
- Patients with CHD and higher baseline ALT levels were more often male and had higher liver stiffness measurements (LSM), higher HDV RNA levels, and lower hepatitis B surface antigen (HBsAg) levels
- Baseline ALT was not associated with body mass index (BMI), concomitant nucleos(t)ide therapy, or the presence of cirrhosis

Table 2. Demographic and Baseline Disease Characteristics by Baseline HDV RNA Tercile

	Total Cohort (N = 532)	HDV RNA <4.9 $\log_{10}$ IU/mL (n = 176)	HDV RNA ≥4.93 to ≤6.04 $\log_{10}$ IU/mL (n = 177)	HDV RNA >6.04 $\log_{10}$ IU/mL (n = 176)	*P* value
Age, years, mean (SD)	**40 (9)**	**42 (9)**	**40 (9)**	**39 (8)**	**.0093**
Male sex, n (%)	346 (65)	109 (62)	117 (66)	119 (68)	.5171
Race, n (%)					.4414
Asian	58 (11)	19 (11)	14 (8)	24 (14)	
Black or African descent	9 (2)	4 (2)	3 (2)	2 (1)	
White	464 (87)	152 (86)	160 (90)	150 (85)	
BMI, kg/m^2, mean (SD)	25.1 (3.8)	25.4 (3.8)	25.2 (3.9)	24.7 (3.7)	.2678
BMI ≥30 kg/m^2, n (%)	52 (10)	18 (10)	20 (11)	14 (8)	.5923
ALT, U/L, median (Q1, Q3)	**87 (60, 131)**	**77 (54, 114)**	**88 (58, 145)**	**93 (70, 143)**	**.0313**
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	**5.3 (1.3)**	**3.8 (1.0)**	**5.5 (0.3)**	**6.5 (0.4)**	**<.0001**
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	**1.3 (1.4)**	**1.2 (1.5)**	**1.1 (1.2)**	**1.5 (1.4)**	**.0228**
HBsAg, $\log_{10}$ IU/mL, mean (SD)	**3.8 (0.6)**	**3.5 (0.8)**	**3.9 (0.4)**	**4.1 (0.4)**	**<.0001**
HBeAg positive, n (%)	**54 (10)**	**12 (7)**	**13 (7)**	**29 (16)**	**.0052**
Nucleos(t)ide therapy,[a] n (%)	178 (33)	56 (32)	64 (36)	56 (32)	.6076
Prior interferon exposure, n (%)	244 (46)	79 (45)	85 (48)	77 (44)	.7079
LSM, kPa, mean (SD)	13.8 (8.1)	13.4 (8.1)	13.8 (8.5)	14.3 (7.6)	.5888
Cirrhosis present, n (%)	203 (38)	66 (38)	66 (37)	69 (39)	.5731

P values for comparison among HDV RNA terciles used Fisher's exact test or ANOVA. [a]Defined as being on nucleos(t)ide therapy at baseline. HDV GT-1 was the most common (n = 501, 94%) followed by HDV GT-2 (n = 5, 1%), HDV GT-5 (n = 5, 1%), and HDV GT-6 (n = 1, 0%); missing (n = 19). HBV genotype, n (%): genotype A, 36 (7); genotype C, 1 (0); genotype D, 296 (56); genotype E, 3 (1); genotype H, 1 (0); missing, 195 (37). ALT, alanine aminotransferase; ANOVA, analysis of variance; BMI, body mass index; GT, genotype; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; LSM, liver stiffness measurements; Q, quartile.

- Patients with CHD and higher HDV RNA tended to be younger, HBeAg positive, and had higher ALT and HBsAg levels
- Of note, hepatitis B virus (HBV) DNA levels were higher with increasing HDV RNA (but mean levels remained low) without a significant difference in concomitant nucleos(t)ide therapy use
- HDV RNA level was not associated with BMI, nucleos(t)ide therapy, or the presence of cirrhosis

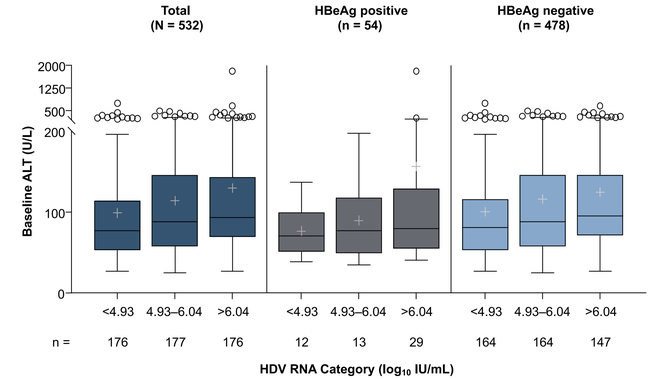
Table 3. Demographics and Baseline Characteristics by HBeAg Status

	Total Cohort (N = 532)	HBeAg (+) (n = 54)	HBeAg (−) (n = 478)	*P* value
Age, years, mean (SD)	40 (9)	40 (10)	40 (9)	.6017
Male sex, n (%)	346 (65)	39 (72)	307 (64)	.2926
Race, n (%)				.4812
Asian	58 (11)	3 (6)	55 (12)	
Black or African descent	9 (2)	1 (2)	8 (2)	
White	464 (87)	50 (93)	414 (87)	
BMI, kg/m^2, mean (SD)	25.1 (3.8)	25.0 (3.9)	25.1 (3.8)	.8232
BMI ≥30 kg/m^2, n (%)	52 (10)	6 (11)	46 (10)	.6356
ALT, U/L, median (Q1, Q3)	87 (60, 131)	77 (56, 123)	90 (61, 134)	.5727
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	**5.3 (1.3)**	**5.8 (1.2)**	**5.2 (1.3)**	**.0021**
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	**1.3 (1.4)**	**2.7 (2.6)**	**1.1 (1.1)**	**<.0001**
HBsAg, $\log_{10}$ IU/mL, mean (SD)	**3.8 (0.6)**	**4.2 (0.4)**	**3.8 (0.6)**	**<.0001**
Nucleos(t)ide therapy,[a] n (%)	**178 (33)**	**29 (54)**	**149 (31)**	**.0013**
Prior interferon exposure, n (%)	244 (46)	23 (43)	221 (46)	.6668
LSM, kPa, mean (SD)	13.8 (8.1)	13.1 (7.0)	13.9 (8.2)	.4919
Cirrhosis present, n (%)	203 (38)	21 (39)	182 (38)	>.9999

P values for comparison between HBeAg groups used Fisher's exact test or ANOVA. [a]Defined as being on nucleos(t)ide therapy at baseline. HDV GT-1 was the most common (n = 501, 94%) followed by HDV GT-2 (n = 5, 1%), HDV GT-5 (n = 5, 1%), and HDV GT-6 (n = 1, 0%); missing (n = 19). ALT, alanine aminotransferase; ANOVA, analysis of variance; BMI, body mass index; GT, genotype; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; LSM, liver stiffness measurements; Q, quartile.

- HBeAg-positive patients with CHD were more likely to be receiving concomitant nucleos(t)ide therapy at baseline
- HBeAg-positive patients with CHD did not have higher mean ALT compared to HBeAg-negative patients with CHD despite higher HBV DNA, HDV RNA, and HBsAg levels

Figure 1. Boxplot of ALT Distribution by HDV RNA Category



Crosses represent the mean. The horizontal lines in the shaded boxes represent the median. The boxes represent the interquartile range (25%–75%). The top and bottom of the lines represent 1.5 times the interquartile range. Points outside of the lines are outliers. Three patients in the HBeAg-negative group had missing data.
ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HDV, hepatitis delta virus.

- Baseline ALT levels increased in similar fashion with increasing HDV RNA levels among HBeAg-positive and -negative patients with CHD