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P3
Poster for you

Value and kinetics of virological markers in the natural course of chronic hepatitis D virus infection

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Background & Aim:

- Chronic hepatitis D virus (HDV) infection can cause severe liver disease.
- In the light of new treatment options, it is of particular importance to identify patients at risk for liver-related complications.
- We aimed to **investigate the kinetics and predictive value of novel virological and immunological markers in the natural course** of chronic HDV infection.

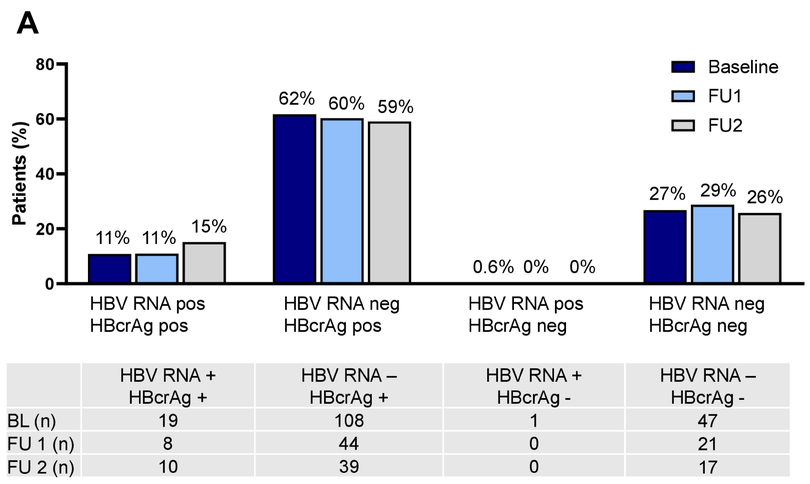
Methods:

- **HBcrAg, HBV RNA** and **quantitative anti-HBc** were analyzed in samples from patients with chronic HDV infection at **three consecutive time points** to study kinetics in the natural course of infection. **Antiviral treatment conditions had to be similar** at all study time points. Results were linked to **clinical outcome.**
- The primary endpoint was the **composite endpoint of any liver-related event** (hepatic decompensation, hepatocellular carcinoma, liver transplantation or liver-related death).
- Assays used in the study: HBV RNA: Roche Cobas 6800, LLOQ 10 cp/ml; HBcrAg: Lumipulse® G Fujirebio-Europe, LLOQ 3 log U/ml; Anti-HBc: Lumipulse® G Fujirebio-Europe, LLOQ 1 IU/ml; HDV RNA: RoboGene HDV RNA quantification kit 2.0 Roboscreen, LLOQ 82 IU/ml

Results:

Total, n	190
Male, n (%)	124 (65)
Age, years	41.3 (32.4-49.7)
HDV RNA (log IU/ml)	4.3 (2.55-5.54)
HDV RNA undetectable, n (%)	31 (16)
HBcrAg (log U/ml)	3.9 (2.9-4.73)
- HBcrAg ≥ 3 log U/ml, n (%)	141 (74)
- HBcrAg < 3 log U/ml or undetectable, n (%)	49 (26)
HBV RNA (cop/ml)#	0 (0-10)
- HBV RNA ≥ 10 cop/ml, n (%)	20 (11)
- HBV RNA < 10 cop/ml or undetectable, n (%)	155 (89)
anti-HBc (IU/ml)	469 (123.5-1570)
HBV DNA (IU/ml)	20 (0-58.2)
HBsAg (IU/ml)	8490 (2250-14032)
HBeAg positive, n (%) §	25 (14)
ALT (U/L)	64 (38-132)
AST (U/L)	64 (40-94)
Platelets (x1000/µl)	135 (64-184.3)
Cirrhosis, n (%)	98 (52)
NA treatment, n (%)	82 (43)
Previous IFN treatment, n (%)	67 (35)
Total follow-up time (years)	2.69 (1.13-6.51)

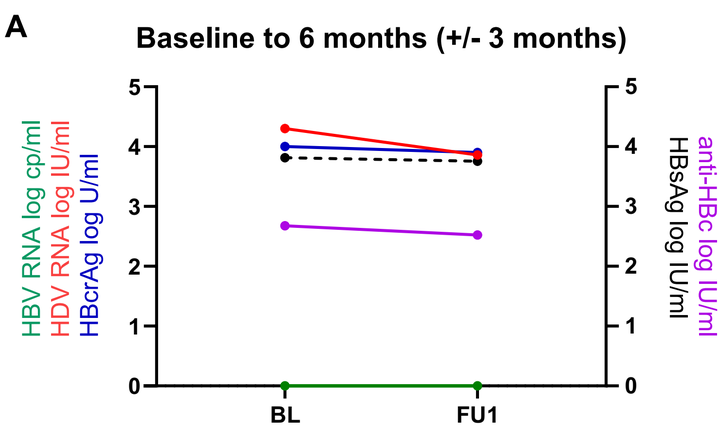
Table 1. Baseline characteristics. Continuous parameters are depicted as median with IQR, categorical variables as number with percentage. #available for 175 patients, §available for 183 patients



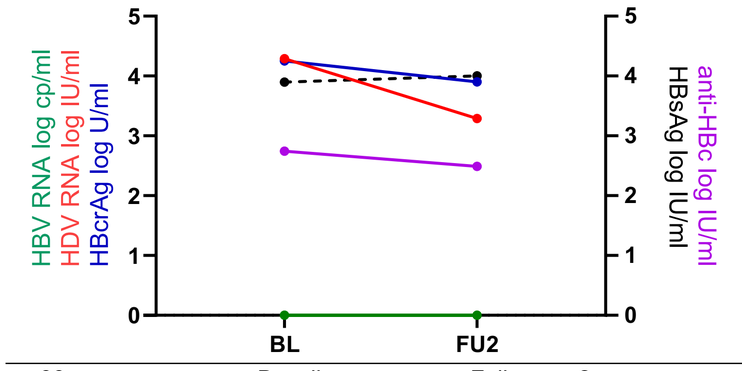
	HBV RNA + HBcrAg +	HBV RNA – HBcrAg +	HBV RNA + HBcrAg -	HBV RNA – HBcrAg -
BL (n)	19	108	1	47
FU 1 (n)	8	44	0	21
FU 2 (n)	10	39	0	17

	HBV RNA + HBcrAg +	HBV RNA – HBcrAg +	HBV RNA + HBcrAg -	HBV RNA – HBcrAg -
BL (n)	8	91	0	46
FU 1 (n)	4	43	0	19
FU 2 (n)	4	33	0	16

Figure 2: Proportion of all (A) or HBeAg-negative (B) patients with concordant or discordant levels of HBcrAg or HBV RNA at study time points. Undetectable HBcrAg is defined as HBcrAg < 3 U/ml, undetectable HBV RNA is defined as HBV RNA < 10 IU/ml.



n=73	Baseline	Follow-up 1	p-value
HDV RNA (log IU/ml)	4.36 (1.44-5.2)	3.86 (0-5.48)	0.1010
HBcrAg (log U/ml)	4.0 (2.85-4.60)	3.9 (2.0-4.65)	**0.0142**
HBV RNA (cop/ml)	0 (0-1)	0 (0-1)	0.3026
anti-HBc (IU/ml)	474 (69-1870)	332 (58-1505)	**0.0018**
HBsAg (IU/ml)	6549 (1788-14025)	5679 (1613-12630)	0.2119



n=66	Baseline	Follow-up 2	p-value
HDV RNA (log IU/ml)	4.29 (2.04-5.2)	3.29 (1.27-5.12)	**0.0041**
HBcrAg (log U/ml)	4.25 (3.0-5.1)	3.9 (2.68-4.9)	**0.0003**
HBV RNA (cop/ml)	0 (0-1)	0 (0-1)	0.0984
anti-HBc (IU/ml)	553 (127-1815)	310 (70-1073)	**<0.0001**
HBsAg (IU/ml)	7899 (2490-14177)	10069 (4213-18572)	0.2424

Figure 1: Comparison of median levels of virological parameters from baseline to FU1 (A) and baseline to FU2 (B). Median levels with interquartile range are depicted in the tables. Wilcoxon signed-rank test was used for comparison of medians.

	Development of the combined endpoint			Multivariable analysis: Model A			Multivariable analysis: Model B		
	No (128)	Yes (62)	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Male, n (%)	79 (62)	45 (73)	0.140						
Age, years	**38.1 (29.1-44.8)**	**50.1 (41.4-57.0)**	**<0.001**	**1.064**	**1.036-1.094**	**<0.001**	**1.063**	**1.034-1.092**	**<0.001**
Cirrhosis, n (%)	**42 (33)**	**56 (90)**	**<0.001**	**7.739**	**3.239-18.49**	**<0.001**	**7.355**	**3.112-17.38**	**<0.001**
NA treatment	50 (39)	32 (52)	0.101						
IFN prior to BL	47 (37)	20 (32)	0.546						
HBV RNA (log cop/ml)#	0 (0-1)	0 (0-1)	0.764						
HBV RNA detectable #	17 (14)	3 (6)	0.093						
HBcrAg (log U/ml)	3.85 (2.63-4.7)	3.95 (3.08-4.8)	0.459						
HBcrAg detectable	93 (73)	48 (77)	0.482						
Anti-HBc (IU/ml)	587 (176-2246)	214 (51-667)	<0.001	1.0	1.0-1.0	0.3341			
HBcrAg/anti-HBc ratio	1.40 (0.97-1.85)	1.69 (1.24-2.31)	0.002				1.096	0.8444-1.423	0.4899
HBsAg (IU/ml) §	8628 (2114-14071)	7016 (2250-12636)	0.593						
HDV RNA (log IU/ml)	4.19 (1.15-5.56)	4.78 (3.26-5.54)	0.184						
HDV RNA detectable	102 (80)	57 (92)	0.032	2.094	0.7928-5.532	0.1358	1.747	0.6845-4.461	0.2431

Table 2. Uni- and multivariate analysis of baseline characteristics of patients with and without the development of the combined endpoint (decompensation, HCC, LTx/death) during follow-up. Continuous parameters are depicted as median with IQR, categorical variables as number with percentage. Mann Whitney U test, Chi-Square or Fisher's exact test were used for group comparison. Multivariable Cox regression was used to address independent association of variables with the development of the combined endpoint during follow-up. # available for 120 and 55, respectively § available for 92 and 40, respectively

	Development of the combined endpoint			Multivariable analysis		
	No (n=42)	Yes (n=56)	p-value	Hazard ratio	95% CI	p-value
Male, n (%)	29 (69)	40 (71)	0.798			
Age, years	**41.5 (33.2-47.6)**	**50.1 (41.4-55.3)**	**<0.001**	**1.046**	**1.008-1.087**	**0.019**
NA treatment	20 (48)	29 (52)	0.683			
IFN prior to BL	14 (33)	18 (32)	0.901			
HBV RNA (log cop/ml)#	0 (0-0)	0 (0-0.25)	0.328			
HBV RNA detectable#	3 (7)	2 (4)	0.654			
HBcrAg (log U/ml)	3.8 (3.0-4.6)	3.85 (3.03-4.68)	0.752			
HBcrAg detectable	33 (79)	43 (77)	0.834			
Anti-HBc (IU/ml)	**433 (127-1335)**	**214 (51-644)**	**0.047**	**1.0**	**1.0-1.0**	**0.014**
HBcrAg/anti-HBc ratio	1.45 (1.11-1.95)	1.67 (1.23-2.28)	0.102			
HBsAg (IU/ml) §	88818 (1419-11756)	7016 (2250-12608)	0.835			
HDV RNA (log IU/ml)	4.02 (1.53-5.46)	4.63 (3.01-5.46)	0.309			
HDV RNA detectable	34 (81)	51 (91)	0.144			
Sodium mmol/L	140 (137-141)	139 (137-141)	0.639			
Creatinine µmol/L	69 (59-80)	66 (55-74)	0.117			
AST U/L	**63 (38-89)**	**80 (56-105)**	**0.015**	**1.009**	**1.004-1.014**	**<0.001**
ALT U/L	58 (36-117)	57 (38-105)	1.0			
gGT U/L	74 (36-159)	71 (35-129)	0.909			
AP U/L	**94 (69-128)**	**143 (106-172)**	**<0.001**	**1.005**	**1.001-1.010**	**0.011**
CHE kU/L	**5.19 (3.95-6.91)**	**3.47 (2.48-4.45)**	**<0.001**	**0.483**	**0.361-0.646**	**<0.001**
Bilirubin mmol/L	**11 (9-19)**	**20 (16-46)**	**<0.001**	**1.006**	**1.0-1.012**	**0.043**
Albumin g/L	40 (36-41)	33 (28-36)	<0.001			
Platelets x1000/µl	**84 (49.5-146.5)**	**58 (48-96)**	**0.023**	**1.0**	**1.0-1.0**	**0.021**
INR	1.17 (1.09-1.26)	1.4 (1.23-1.63)	<0.001			

available for 91 samples § available for 68 samples

Table 3. Comparison of baseline characteristics of patients with liver cirrhosis with and without the development of the combined endpoint during follow-up.

Continuous parameters are depicted as median with IQR, categorical variables as number with percentage.

Mann Whitney U test, Chi-Square or Fisher's exact test were used for group comparison.

Multivariable analysis was performed by cox regression analysis.

Due to the strong baseline correlation between INR and CHE (0.639), and CHE and albumin (0.677) only CHE was included in the multivariable model.

Conclusion:

- In this well-characterized cohort of 190 HDV-infected patients with a long follow-up, neither baseline levels nor kinetics of HBcrAg, HBV RNA or quantitative anti-HBc were independently associated with clinical outcome.
- Stage of liver disease and age were predictors of liver-related events.
- Quantitative anti-HBc was significantly lower in patients with liver cirrhosis and especially in those developing liver-related endpoints.
- This encourages further research, particularly in the context of antiviral treatment that aims to achieve immunological control.

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