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HBs isoforms as innovative biomarkers in predicting virological response in chronic hepatitis delta patients treated with bulevirtide monotherapy

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Introduction

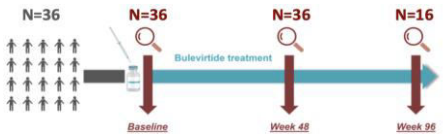
- HDV exploits the HBV surface protein (HBsAg) for the release of its progeny and entry into hepatocytes.
- HBsAg consists of three different proteins: Large (L-HBs), including preS-1, preS-2 and S regions; Middle (M-HBs), including pre-2 and S regions, and small HBsAg (S-HBs), containing only the S region.
- L-HBs is mainly present in virions and is crucial for the binding to the NTCP receptor and thus for entry into the hepatocytes while M-HBs' role is still enigmatic.

Aim

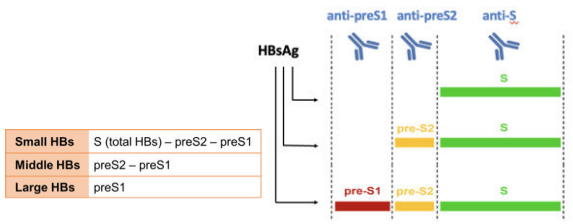
- To investigate the still unknown kinetics of HBs isoforms in patients receiving the entry inhibitor bulevirtide (BLV).

Methods

- 36 consecutive patients with HDV-related compensated cirrhosis and under effective NUC treatment starting BLV monotherapy 2mg/day were enrolled in this single centre retrospective/longitudinal study.



- L-HBs, M-HBs and S-HBs were quantified by ad hoc ELISAs (Beacle Inc.) at baseline and at week 48 (W48) for all patients and at week 96 (W96) for a subset of 16 patients.



- Virological response to BLV was defined as HDV-RNA undetectable or >2log decline compared to baseline, biochemical response as ALT normalization, while combined response as the achievement of both virological and biochemical responses.

Results

Patients' characteristics at baseline

Variables	Patients (N=36)
Age, median (IQR) years	51 (40-62)
Male, N (%)	20 (55.6%)
Liver stiffness measurements, median (IQR) kPa	17.5 (15.1-32.8)
ALT, median (IQR) U/l	102 (65-152)
Platelets, median (IQR) x 10^3/mm^3	70 (59-92)
NUC treatment, N (%)	36 (100%)
HBV-DNA <20 IU/ml, N (%)	36 (100%)
HDV-RNA, median (IQR) logIU/ml	5.1 (4.3-5.7)

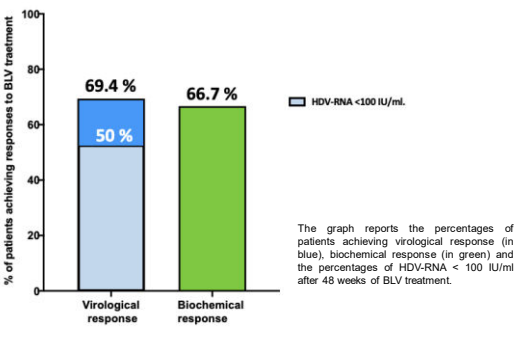
HBs isoforms at baseline

Variables	Patients (N=36)
Total HBsAg, median (IQR) IU/ml [a]	5265 (2338-9105)
Total HBsAg, median (IQR) ng/ml[b]	5296 (1630-8868)
S-HBs, median (IQR) ng/ml	3681 (1240-7184)
M-HBs, median (IQR) ng/ml	813 (260-2262)
L-HBs, median (IQR) ng/ml	5 (1-12)

[a] The values reported are determined by commercial assay.
[b] The values reported are determined by the the kit HBs S Antigen Quantitative ELISA Kit, Rapid-II (Beacle Inc.).

Response to BLV treatment

After 48 weeks of BLV treatment, serum HDV-RNA declined by 3.1 (1.6-3.7) log IU/ml and virological and biochemical responses were observed in 69.4% (25/36) and 66.7% (24/36) of patients, respectively. At week 48 of BLV treatment, 50% (18/36) of patients had a serum HDV-RNA <100 IU/ml.



The graph reports the percentages of patients achieving virological response (in blue), biochemical response (in green) and the percentages of HDV-RNA < 100 IU/ml after 48 weeks of BLV treatment.

Changes of HBs isoforms at weeks 48 and 96

At 48 weeks of BLV treatment, a decline of at least 10% as compared to baseline was noted in 52.7%, 52.7% and 30.6% of patients for S-HBs, M-HBs and L-HBs, respectively (median [IQR] decline: 1323 [731-3712], 327 [79-589] and 10 [4-14] ng/ml for S-HBs, M-HBs and L-HBs).

At 96 weeks of BLV treatment, a decline of at least 10% as compared to week 48 was noted in 43.8%, 31.3% and 37.5% of patients for S-HBs, M-HBs and L-HBs, respectively (median [IQR] decline: 1178 [384-3538], 250 [188-565] and 3 [2-3] ng/ml for S-HBs, M-HBs and L-HBs).

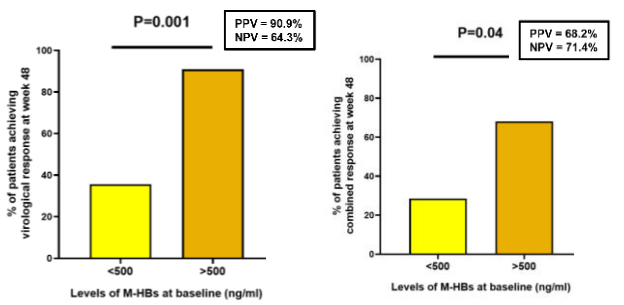
HBs isoforms	% of patients with >10% decline	
	From baseline to week 48	From week 48 to week 96
S-HBs	52.7%	43.8%
M-HBs	52.7%	31.3%
L-HBs	30.6%	37.5%
	Median (IQR) decline in ng/ml [a]	
	From baseline to week 48	From week 48 to week 96
S-HBs	1323 (731-3712)	1178 (384-3538)
M-HBs	327 (79-589)	250 (188-565)
L-HBs	10 (4-14)	3 (2-3)

[a] Median (IQR) values were calculated on the percentages of patients with HBs forms decline of at least 10% at week 48 and 96 of BLV of at least 10% respect to baseline and to week 48, respectively.

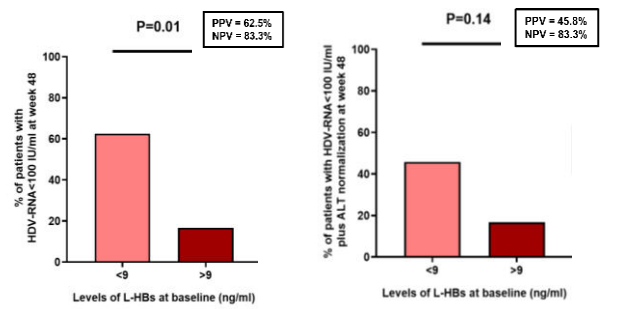
Role of HBs isoforms as biomarkers in predicting virological response to BLV

M-HBs levels >500 ng/ml were associated with virological response at week 48 of treatment (PPV=90.9% and NPV=64.3%, P=0.01). M-HBs levels >500 ng/ml were also associated with the achievement of combined response (PPV=68.2%, NPV=71.4%, P=0.04).

L-HBs levels <9 ng/ml at baseline were significantly correlated with the achievement of HDV-RNA <100 IU/ml at week 48 of BLV treatment (PPV=62.5%, NPV=83.3%, P=0.01) and showed a trend towards the achievement of serum HDV-RNA <100 IU/ml plus ALT normalization (PPV=45.8%, NPV=83.3%, P=0.14).



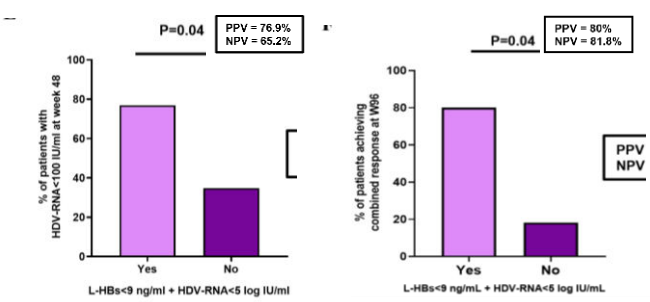
The graphs report the percentage of patients at week 48 of BLV therapy achieving virological response or combined response according to baseline M-HBs levels. Statistically significant differences were assessed by Fisher exact test. Abbreviations: PPV, positive predictive value; NPV, negative predictive value.



The graphs report the percentage of patients at week 48 of BLV therapy achieving HDV-RNA <100 IU/ml or HDV-RNA <100 IU/m with ALT normalization according to baseline L-HBs levels. Statistically significant differences were assessed by Fisher exact test. Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

The combination of pre-treatment L-HBs <9 ng/ml plus serum HDV-RNA <5 log IU/ml was the best predictor for the achievement of serum HDV-RNA <100 IU/ml after 48 weeks of BLV treatment (PPV=76.9%, NPV=65.2%, P=0.04).

The combination of pre-treatment L-HBs <9 ng/ml plus plasma HDV-RNA <5 log IU/ml also proved to be the best predictor for achieving combined response after 96 weeks of BLV treatment (PPV=80%, NPV=81.8%; P=0.04).



The graphs report the percentage of patients achieving HDV-RNA <100 IU/ml at week 48 of BLV therapy or combined response at week 96 according to both L-HBs and HDV-RNA levels at baseline. Statistically significant differences were assessed by Fisher exact test. Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

Conclusion

Quantification of HBs isoforms along with serum HDV-RNA can reflect more accurately the burden of circulating infectious virions, thus representing a new promising tool to identify patients more likely to respond to bulevirtide monotherapy.