Kinetics of the three HBsAg isoforms along with HDV-RNA predict virological response in CHD patients treated with bulevirtide up to 96 weeks

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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 preS1, preS2 and S regions; Middle (M-HBs), including pre-Z 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.
- Here, we investigate the still unknown kinetics of HBsAg forms in patients receiving the entry inhibitor bulevirtide.

Study Design
- Twenty consecutive patients with HDV-related compensated cirrhosis starting bulevirtide monotherapy 2mg/day were enrolled in this single-center retrospective/longitudinal study.
- All patients were under effective NUC treatment at entry.

Methods
- L-HBs, M-HBs and S-HBs were quantified by ad hoc ELISAs (Beacle Inc.) at baseline and week 48 (W48) for all patients and at week 96 (W96) for a subset of 16 patients.
- HDV-RNA was quantified by Robogene 2.0 (LoD:6 IU/mL).

Results

Patients’ characteristics at baseline

<table>
<thead>
<tr>
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<th>N=20</th>
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<tbody>
<tr>
<td>Age in years, median (IQR)</td>
<td>50 (40–62)</td>
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<tr>
<td>Male sex, N (%)</td>
<td>13 (65%)</td>
</tr>
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<td>Liver stiffness measurement in kPa, median (IQR)</td>
<td>17.6 (13.1–20.4)</td>
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<td>ALT in U/L, median (IQR)</td>
<td>110 (85–147)</td>
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<td>Platelets x 10^9/mL, median (IQR)</td>
<td>72 (59 – 80)</td>
</tr>
<tr>
<td>Serum HBV-RNA in log IU/mL, median (IQR)</td>
<td>4.9 (4.4–5.7)</td>
</tr>
<tr>
<td>Serum HBsAg in mg/L, median (IQR)</td>
<td>3.7 (3.2–4.5)</td>
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<tr>
<td>HBsAg forms at baseline</td>
<td></td>
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<tr>
<td><strong>S-HBs</strong></td>
<td>Median (IQR): 962 (1940–8399) µIU/mL, N (%)</td>
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<tr>
<td><strong>M-HBs</strong></td>
<td>Median (IQR): 79.1 (80–1993) µIU/mL, N (%)</td>
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<tr>
<td><strong>L-HBs</strong></td>
<td>Median (IQR): 7.3 (7.2–15) µIU/mL, N (%)</td>
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According to literature (Pfefferkorn, 2021), small-HBs is the most represented HBsAg form as it is involved in the constitution of both mature virions and subviral particles.
- L-HBs is poorly represented as it is contained only in mature virions, where it is responsible for the interaction with the cell receptor.

Response to bulevirtide

- Following bulevirtide treatment, virological response was achieved in 70% (14/20) and 81.2% (13/16) of pts at W48 and W96, while HDV-RNA undetectability in 35% (7/20) and 43.8% (7/16) at W48 and W96.
- In patients with undetectable HDV-RNA, ALT<40U/L was observed in 5/7 and 6/7 patients at these time-points.

HBS forms decline after 48 weeks of treatment

- Following 48 weeks of bulevirtide treatment, S-HBs, M-HBs and L-HBs decreased of at least 10% respect to baseline in 60%, 50% and 40% of patients.

Role of HBs forms and HDV-RNA as biomarkers in predicting virological response to bulevirtide

- A level of L-HBs<9 ng/mL at baseline significantly correlated with the achievement of HDV-RNA undetectability.
- Superimposable result was observed in relation to the achievement of HDV-RNA undetectability plus ALT normalization.

Conclusion

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