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Poster for you

Plasma pre-S1 HBsAg levels during antiviral therapy with Bulevirtide in chronic hepatitis delta patients – any help in predicting response to therapy?

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Introduction

- The HBV envelope comprises LHBS, MHBS and SHBS proteins.
- Large HBsAg mediates HBV attachment to the NTCP receptor and entry into hepatocytes and is critical to the propagation of hepatitis delta virus (HDV).
- Pre-S1 LHBS protein originates from both covalently closed circular DNA (cccDNA) and integrated HBV DNA.
- Bulevirtide (BLV) mimics a pre-S1 HBsAg protein and blocks entry to hepatocytes (1).
- While HBsAg concentrations are not affected during antiviral therapy with BLV, there is only limited data comparing changes in plasma pre-S1 HBsAg protein levels during Bulevirtide therapy(2).

Study Design/ Aims

We aimed to measure and compare levels of pre-S1 HBsAg during therapy with bulevirtide and assess their changes in relation to HDV RNA decline and/or ALT normalisation.

Materials & Methods

- Blood samples were collected from 14 HBV/HDV co-infected patients treated with Bulevirtide (all HDV RNA positive, median age 45 years, 8 males, 79% compensated cirrhosis).
- Plasma was collected at three time points (therapy start, week 12 & 24), and the following HBV/HDV biomarkers were measured:
  - **Total HBsAg** (Abbott Architect® assay, IU/ml),
  - **Pre-S1 levels** (Abbkine ELISA, IU/ml]),
  - **HDV RNA** (Abbott Diagnostics research use only mRealTime assay, LLoQ =5 IU/ml) (3)
- The proportion of pre-S1 HBsAg [%] was determined using total HBsAg concentration.
- Up-to-date, 10 patients have completed 24 weeks of BLV therapy.

The response to BLV at week 24 (compared to therapy start) was categorised as:

- **Responder (R)**: decline >2 $\log_{10}$IU/ml,
- **Partial responder (PR)**: drop 1-2 $\log_{10}$IU/ml
  Non-responder (NR): decline < 1 $\log_{10}$ IU/ml

Results baseline

Baseline levels of total HBsAg, pre-S1 HBsAg and HDV RNA were not predictive of a sharp HDV RNA decline (>2 $\log_{10}$) or ALT normalisation at week 12 and/or 24.

Results therapy start vs. week12

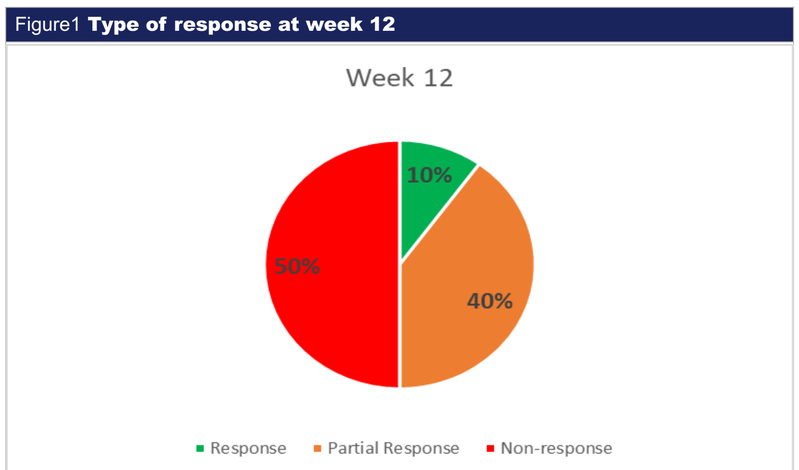
One patient (10%) achieved HDV RNA decline >2 $\log_{10}$ vs. 4 patients (40%) with partial response (1-2 $\log_{10}$) and 5 patients (50%) with a slow HDV RNA decline <1 $\log_{10}$ (Figure 1).

Four (40%) patients had normal ALT.

There was no significant change in:

- total HBsAg (9082 vs 9434 IU/ml, p=0.8),
- pre-S1 HBsAg levels (55.3 vs 55.2 IU/ml, p=0.5),
- proportion of total HBsAg (1.72% vs 1.67%, p=0.65).

Figure1 **Type of response at week 12**



Results therapy start vs. Week 24

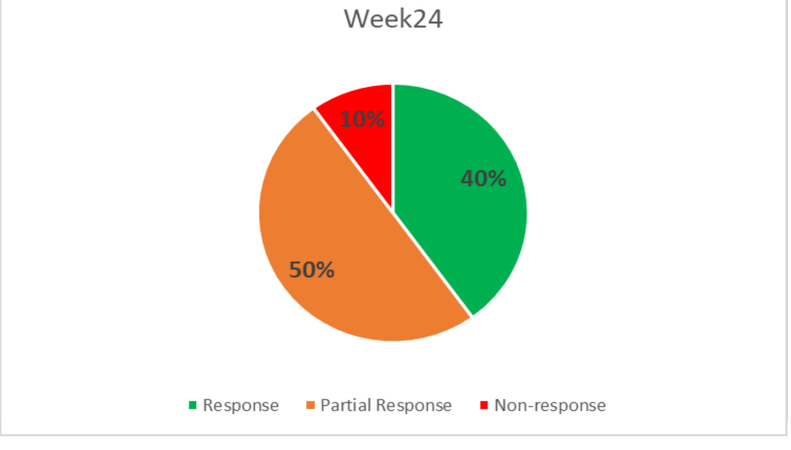
Four (40%) patients achieved >2 $\log_{10}$ HDV RNA decline, 5 (50%) patients had HDV RNA decline 1-2 $\log_{10}$ and 1 (10%) patient with a slow decline <1 $\log_{10}$ (Figure 2).

Five (50%) patients had normal ALT.

While total HBsAg levels were similar (9082 vs. 9389 IU/ml, p=0.67), there was a significant increase in median of pre-S1 HBsAg levels to 63 IU/ml (p=0.04) and in proportion of total HBsAg 1.98% (p=0.05).

These were similar irrespective of type of response to BLV therapy.

Figure 2 **Type of response at week 24**



Results of HBsAg, pre-S1 & HDV levels during Bulevirtide therapy

Figure 3 **Total HBsAg levels during bulevirtide therapy**

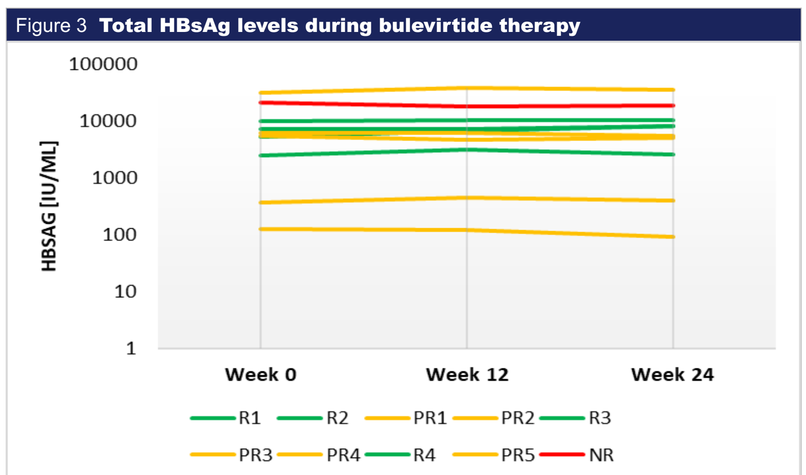


Figure 4 **Pre-S1 levels during bulevirtide therapy**

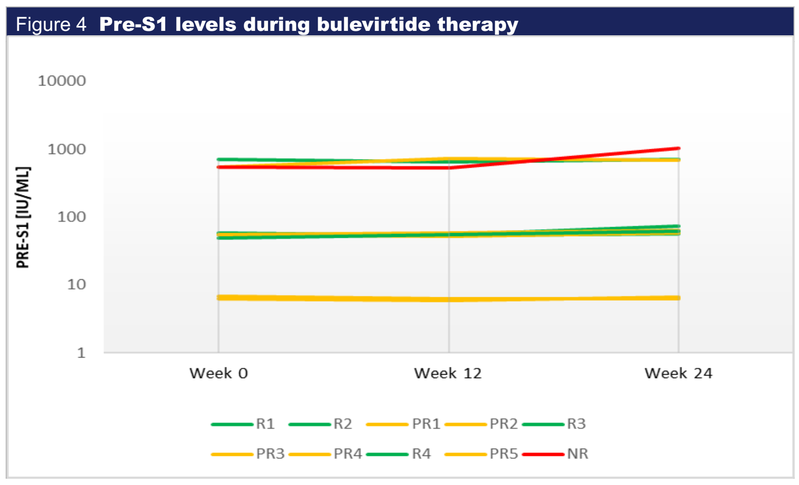


Figure 5 **Proportions of pre-S1 vs. total HBsAg during bulevirtide therapy**

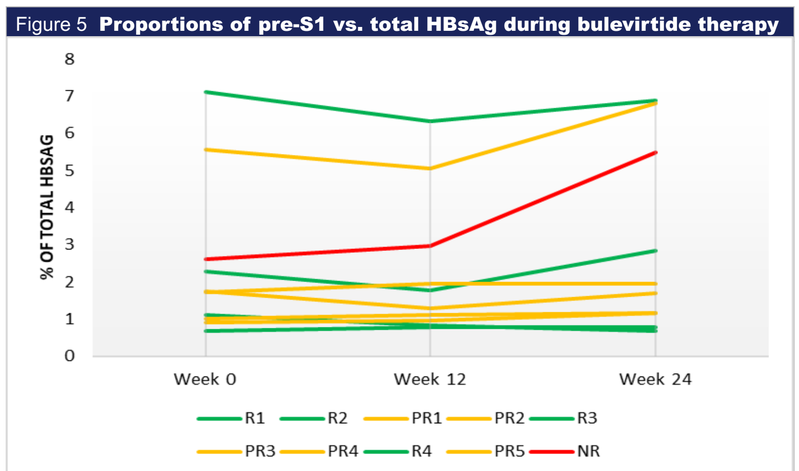
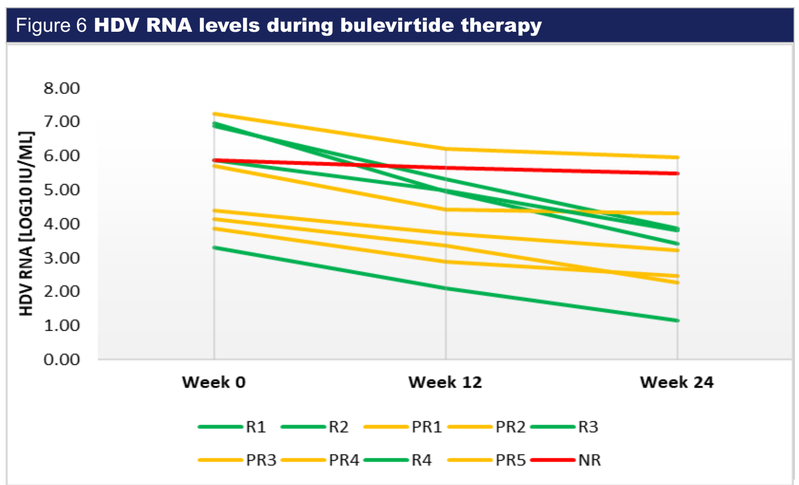


Figure 6 **HDV RNA levels during bulevirtide therapy**



Conclusion

While concentrations of total HBsAg did not change significantly during therapy with Bulevirtide, pre-S1 HBsAg levels increased in all patients between week 12 and 24 of therapy with Bulevirtide.

The meaning of changes in pre-S1 HBsAg plasma during therapy is unexplained, but Bulevirtide mimics a pre-S1 HBsAg protein and blocks viral entry to hepatocytes and pre-S1 HBsAg expression in the liver was not tested.

It is not clear whether this reflects the existing state of viral interference between HBV and HDV and more studies assessing the role of this serological biomarker with Bulevirtide HDV treatment would be helpful.

Reference

1. NICE Guidance: Bulevirtide for treating chronic hepatitis D. www.nice.org.uk/guidance/TA896
2. EASL Clinical Practice Guidelines on hepatitis delta virus. J Hepatol 2023
3. Coller KE et al Scientific Reports 2018