OCTOBER 11-12, 2024 MILAN, ITALY
DeltaCure 3rd International Meeting
P59
Poster for you

Dichotomy between HBcrAg and pre-genomic HBV RNA in relation to HDV RNA response in patients with chronic hepatitis delta during bulevirtide treatment

Cargill Z, Anderson M, Shah S, Lok J, Cloherty G, Dusheiko G, Agarwal K & Carey I

Introduction

- HBsAg mediates HBV attachment to the NTCP receptor and entry into hepatocytes and is critical to the propagation of hepatitis delta virus (HDV).
- HBsAg originates from both covalently closed circular DNA (cccDNA) and integrated HBV DNA.
- Hepatitis B core-related antigen (HBcrAg) and pre-genomic HBV RNA (pgRNA) reflect cccDNA transcriptional activity (1).
- Bulevirtide (BLV) mimics a pre-S1 HBsAg protein and blocks entry to hepatocytes (2).
- While HBsAg concentrations are not affected during Bulevirtide therapy, there is limited data comparing changes in HBcrAg and pgRNA during Bulevirtide therapy (3).

Study Design/ Aims

We aimed to compare levels of HBV markers (HBV DNA, HBsAg, HBcrAg & pgRNA) during Bulevirtide therapy 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:
  - **HBV DNA** (Roche assay, IU/ml),
  - **HBsAg** (Abbott Architect® assay, IU/ml),
  - **HBcrAg** (CLEIA, Fujirebio, $\log_{10}$ U/ml),
  - **pgRNA** (Abbott Diagnostics dual-target real-time-PCR assay, LLoQ= 0.49 $\log_{10}$ U/ml),
  - **HDV RNA** (Abbott Diagnostics research use only mRealTime assay, LLoQ =5 IU/ml) (4)
- 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 HBcrAg, HBsAg, pgRNA, HDV RNA & ALT 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

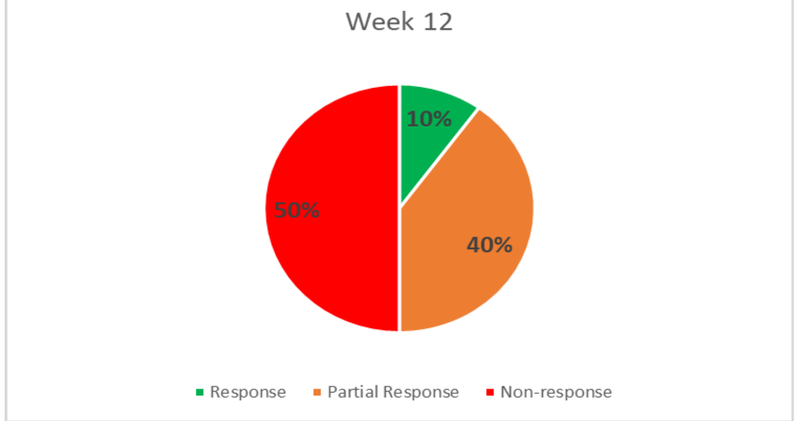
One patient (10%) achieved HDV RNA decline >2 $\log_{10}$ vs. 4 patients (40%) with partial response (1-2 $\log_{10}$) and 5 patients (50%) with a slow HDV RNA decline <1 $\log_{10}$ (Figure 1)

Four (40%) patients had normal ALT

There was a marked reduction in ALT (-38 IU/L, p=0.02), HDV RNA (-1.1 $\log_{10}$ IU/ml, p<0.01) & HBcrAg (-0.8 $\log_{10}$ U/ml, p<0.01), but no significant change in HBsAg (9082 vs 9434 IU/ml, p=0.8) & HBV DNA (0 vs 0 IU/ml, p=1.0).

In contrast, pgRNA markedly increased (0.57 $\log_{10}$ U/ml, p=0.03).

Figure1 **Type of response at week 12**



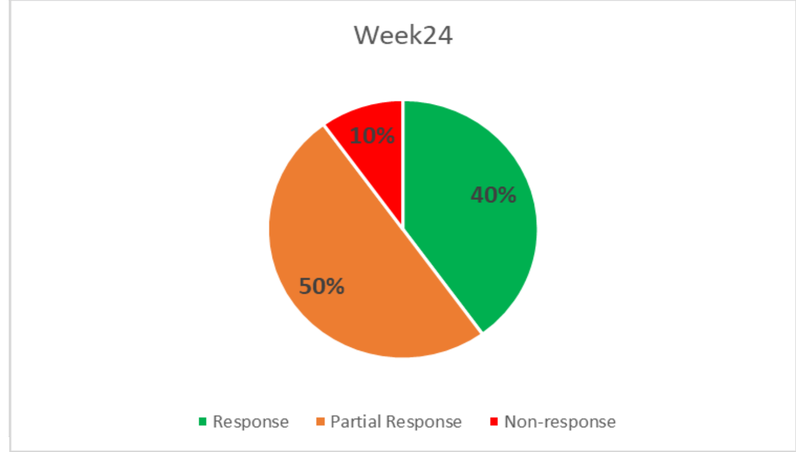
Results therapy start vs. Week 24

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 $\log_{10}$

Five (50%) patients had normal ALT.

There was a significant reduction in ALT (-46 IU/L, p<0.01), HDV RNA (-1.83 $\log_{10}$ IU/ml, p<0.01) and HBcrAg (-1.1 $\log_{10}$ U/ml, p<0.01), but HBsAg (9082 vs. 9389 IU/ml, p=0.67), HBV DNA (0 vs 0 IU/ml, p=1) and pgRNA (1.5 vs 1.58 $\log_{10}$U/ml, p=0.58) levels were similar.

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



Results of HBV & HDV markers

All patients had **HBV DNA** below detection limit of 20 IU/ml in baseline, week 12 and week 24

Figure 3 **HBsAg levels during bulevirtide therapy**

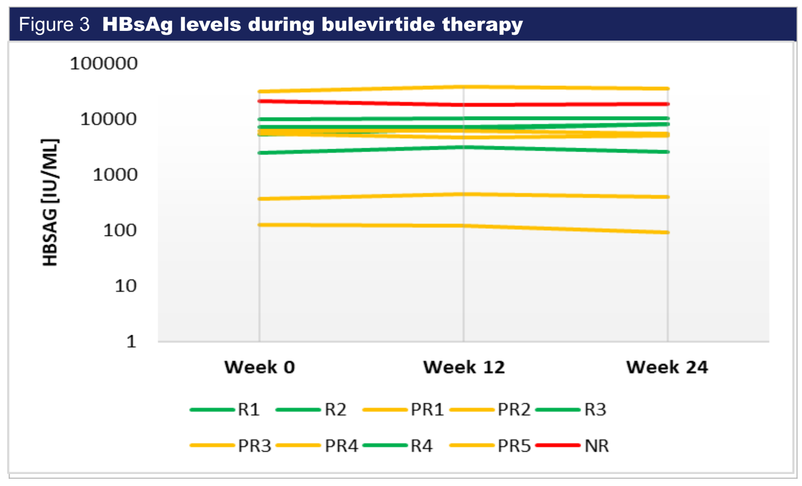


Figure 4 **HBcrAg levels during bulevirtide therapy**

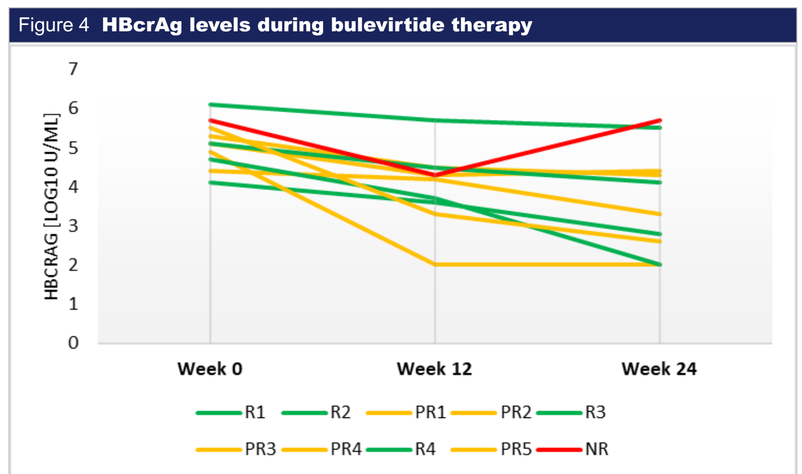


Figure 5 **Pg-RNA levels during bulevirtide therapy**

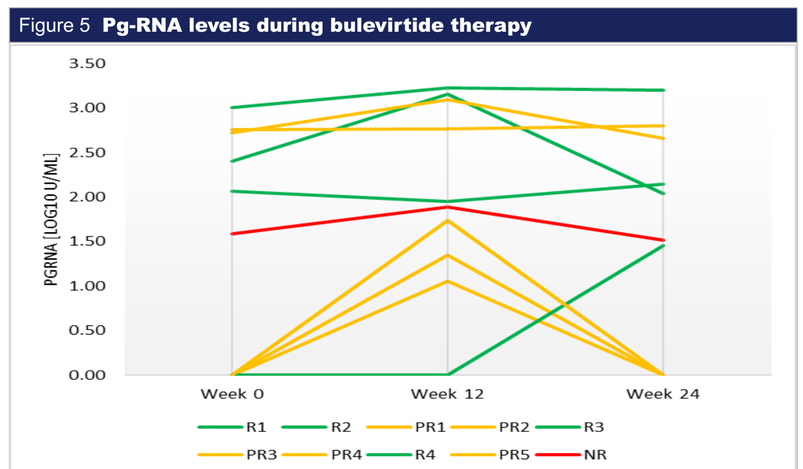
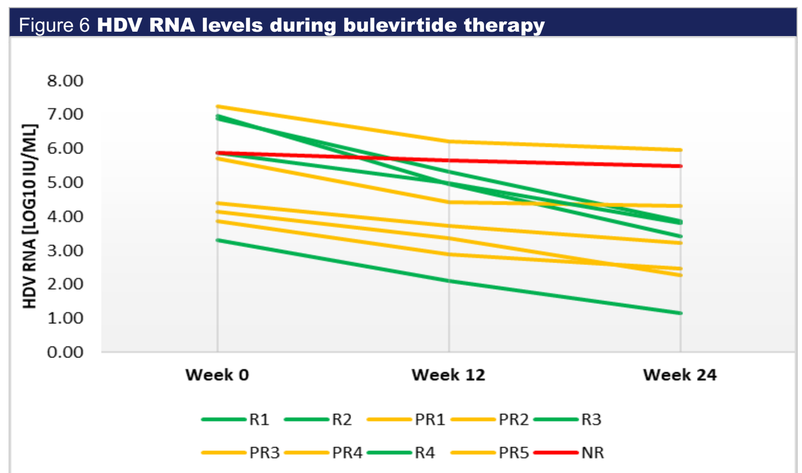


Figure 6 **HDV RNA levels during bulevirtide therapy**



Conclusion

In contrast to HBsAg & HBV DNA, HBcrAg levels mirrored changes in HDV RNA during Bulevirtide therapy.

Pre-genomic RNA increased in the first 12 weeks of therapy followed by a gradual decline by week 24.

The lower HBcrAg and initial pgRNA increase during BLV therapy are unexplained, but could mirror relative differences in expression of HBsAg from residual cccDNA v.s integrated DNA, affecting HDV propagation, as BLV is not a HDV replication/assembly inhibitor.

Reference

1. Lok J et al. Reveiw: Novel biomarkes in hepatitis B. AP&T 2022
2. NICE Guidance: Bulevirtide for treating chronic hepatitis D. www.nice.org.uk/guidance/TA896
3. EASL Clinical Practice Guidelines on hepatitis delta virus. J Hepatol 2023
4. Coller KE et al Scientific Reports 2018