THU302

Bulevirtide Is Broadly Active Against All HDV Genotypes Expressing Envelopes From HBV Genotypes A–H and a Large Panel of Clinical Isolates

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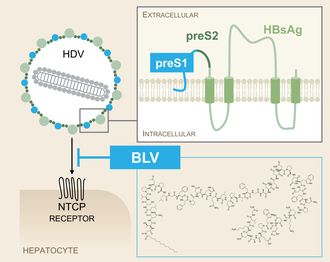
Introduction

Bulevirtide (BLV)



HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; NTCP, sodium taurocholate cotransporting polypeptide.

- BLV is a 47-amino acid lipopeptide derived from the hepatitis B virus (HBV) large envelope protein
- BLV binds to the HDV/HBV host entry receptor NTCP and acts as a potent HDV entry inhibitor[1,2]
- BLV has been approved for treatment of HDV in the EU and is under late-stage clinical evaluation in the United States
- Based on sequence divergence, there are 8 HDV genotypes (HDV-1 to -8) and 8 HBV genotypes (GT A–H), with HDV-1 being the most common globally
- It is necessary for BLV to be active against diverse HDV/HBV sequences to be globally therapeutically effective

Objective

- To assess the antiviral activity of BLV against HDV-1 to -8 with HBV GT A–H envelopes and a large panel of clinical isolates using primary human hepatocytes (PHHs)

Methods

- HDV viruses were produced by cotransfection of Huh7 cells with HDV genome and HBV envelope plasmids
- Subsequently, virus-containing supernatant was collected, titered, and used to infect PHHs
- For the HDV phenotyping assay, PHHs were pretreated with BLV and then infected with clinical plasma or a laboratory strain of HDV
- After 5 d, immunofluorescence staining was performed to determine cells that were positive for HDV antigen
- The BLV concentration that decreased the HDV antigen-positive cells by 50% was expressed as mean half-maximal effective concentration (EC_{50}) from ≥2 independent experiments

Results

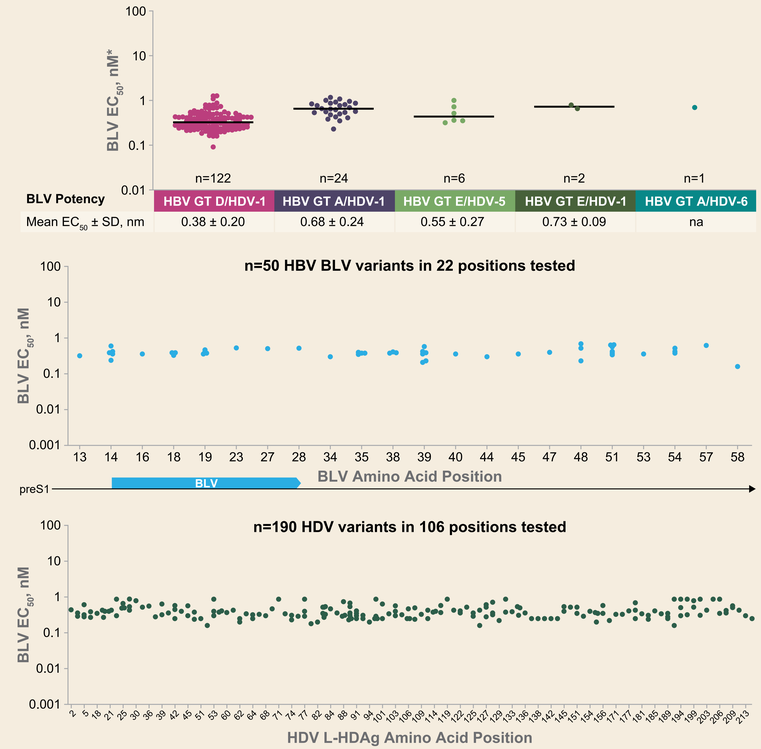
Antiviral Activity of BLV Against HDV-1 to -8 Enveloped With HBV GT A–H

HBV GT	BLV EC_{50}, nM								
	HDV-1	HDV-2	HDV-3	HDV-4	HDV-5	HDV-6	HDV-7	HDV-8	Mean of HBV
A	0.65	0.44	0.32	Failure	0.52	0.48	0.59	0.43	0.49
B	0.60	0.53	0.50	0.71	0.84	0.66	0.82	0.75*	0.67
C	0.46	0.59	0.32	Failure	0.32	0.49	0.46	0.93	0.51
D	0.49	0.23	0.36	Failure	0.52	0.33	0.38	0.38	0.38
E	0.85	0.39	0.54	0.65	0.76	0.65	0.80	0.64	0.66
F	0.28	Failure	0.30	Failure	0.34	ND	0.24	0.52	0.34
G	0.57	0.68	0.76	0.56	0.73	0.67	0.86	0.59	0.68
H	0.45	0.61	0.39	Failure	0.34	ND	0.31	0.56	0.44
Mean of HDV	0.54	0.50	0.44	0.64	0.55	0.55	0.56	0.58	—

*Determined in Stephan Urban's laboratory. ND, not determined.

- Mean EC_{50} values of BLV against HBV GT A–D envelopes pseudotyped HDV-1 to -8 ranged from 0.38 to 0.67 nM
  - Similarly, for HBV GT E–H envelopes pseudotyped HDV-1 to -8, mean EC_{50} values of BLV ranged from 0.34 to 0.68 nM
- Across HDV-1 to -8 enveloped with HBV GT A–H, mean EC_{50} values of BLV ranged from 0.44 to 0.58 nM

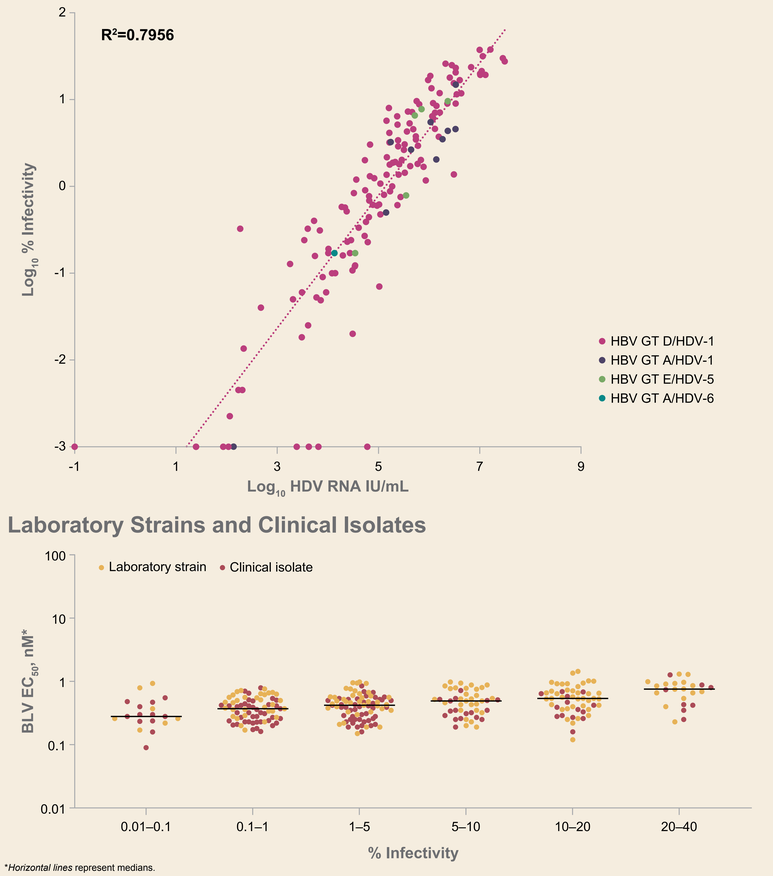
Figure 1. Antiviral Activity of BLV Against HDV Clinical Isolates at Baseline



Horizontal lines represent medians. L-HDAg, large hepatitis delta antigen; na, not applicable; SD, standard deviation.

- Most clinical isolates tested (n=122) belonged to HBV GT D/HDV-1 and were within a narrow range of the median EC_{50} of 0.38 nM
- Regardless of the HBV/HDV GT combination, median EC_{50} values for all clinical isolates tested were similar and ranged from 0.38 to 0.73 nM
- HBV preS1 and L-HDAg amino acid substitutions were tested and found not to be associated with reduced susceptibility to BLV
- Mean EC_{50} values of BLV for HDV-1 enveloped with multiple strains of HBV GT A, B, C, and D carrying commonly observed polymorphisms were 0.57, 0.59, 0.43, and 0.33 nM, respectively (EASL 2022, Poster THU309)

Figure 2. HDV Infectivity Correlated With Viral Titer and Had Minimal Effect on EC_{50}



Horizontal lines represent medians.

- In vitro infectivity in the PHH infection system correlated with HDV viral titer
- Despite a wide range in the infectivity of both laboratory strains and clinical isolates of all combinations of HBV/HDV GT tested, it had minimal effect on EC_{50} values in a PHH infection system (<2-fold)

Conclusion

- In all, 155 clinical isolates and 74 laboratory strains tested in the PHH infection assay were susceptible to BLV, with EC_{50} values in the low nanomolar range
- BLV demonstrated potent broad-spectrum antiviral activity against HDV-1 to -8 enveloped with HBV GT A–H and a larger panel of HDV clinical isolates
- These results support BLV having broad GT coverage potential for the treatment of patients with chronic HDV infection

References: **1.** Ni Y, et al. Gastroenterology 2014;146:1070-83; **2.** Yan H, et al. eLife 2012;1:e00049. **Acknowledgments:** This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by BioScience Communications, New York, New York, USA, funded by Gilead.

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