Persistent Low Viremic Relapse vs High Viremic Relapse After the End of Treatment With Bulevirtide With or Without Pegylated Interferon in Patients With Chronic Hepatitis Delta Virus

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Conclusions

- Of patients treated with bulevirtide (BLV) monotherapy or BLV in combination with pegylated interferon alfa (PegIFNα), 57/131 (44%) had sustained undetectable hepatitis delta virus (HDV) RNA posttreatment
- A small subset (14/131, 11%) of patients had low viremic relapse (positive HDV RNA levels <50 IU/mL) posttreatment and maintained biochemical response with no progression to high viremic relapse through 1 year of posttreatment follow-up
- The remaining patients (60/131, 46%) had high viremic relapse posttreatment, which was associated with alanine aminotransferase (ALT) increases and loss of biochemical response
- The long-term clinical significance of low viremic relapse in the posttreatment period remains unknown, and further study on the durability of response in these patients is needed

Plain Language Summary

- Bulevirtide is used to treat patients with chronic hepatitis delta
- This study analyzed the durability of treatment responses in patients who received bulevirtide alone or in combination with pegylated interferon alfa for at least 96 weeks and then ended treatment
- Almost half of patients who had undetectable hepatitis delta virus at the end of treatment remained virus free during follow-up. Among patients with viral relapse, some maintained stability in markers of liver damage

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Disclosures: Conflict of interest disclosures may be viewed using the QR code at the top right.

Introduction

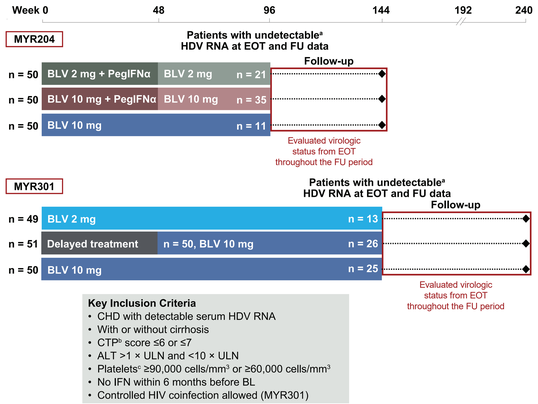
- HDV is a defective RNA virus that requires the presence of hepatitis B surface antigen as its envelope protein for propagation[1,2]
- Infection with HDV causes the most severe form of viral hepatitis and leads to more rapid progression to cirrhosis and an increased risk of hepatocellular carcinoma compared with hepatitis B virus monoinfection[3,4]
- BLV, a first-in-class entry inhibitor of HDV, is approved in the European Economic Area, the United Kingdom, Switzerland, the Russian Federation, Australia, and Canada at 2 mg/day for treatment of chronic hepatitis delta in patients with compensated liver disease[5-7]
- Previous analyses showed that achieving undetectable HDV RNA at end of treatment (EOT) is a predictor of sustained undetectable viremia posttreatment; patients with viremia at any level at EOT are likely to have increased HDV RNA off treatment[8,9]

Objective

- To investigate the posttreatment outcomes in patients with HDV who received BLV 2 or 10 mg monotherapy or combined therapy with PegIFNα, achieved undetectable HDV RNA by EOT, and had low viremic relapse with HDV RNA levels <50 IU/mL compared with those who had sustained undetectable HDV RNA or had high viremic relapse with HDV RNA levels ≥50 IU/mL

Methods

Pooled Analysis: MYR204 and MYR301



Key Inclusion Criteria
- CHD with detectable serum HDV RNA
- With or without cirrhosis
- CTP[b] score ≤6 or ≤7
- ALT >1 × ULN and <10 × ULN
- Platelets[c] ≥90,000 cells/mm^3 or ≥60,000 cells/mm^3
- No IFN within 6 months before BL
- Controlled HIV coinfection allowed (MYR301)

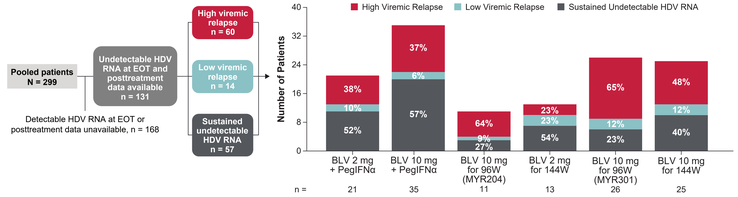
[a]Undetectable HDV RNA was defined as less than the lower limit of quantitation (50 IU/mL; target not detected). [b]MYR204, CTP s6; MYR301, CTP ≤7. [c]MYR204, platelets ≥90,000 cells/mm^3; MYR301, platelets ≥60,000 cells/mm^3.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; CHD, chronic hepatitis delta; CTP, Child-Turcotte-Pugh; EOT, end of treatment (W144); FU, follow-up; HDV, hepatitis delta virus; IFN, interferon; PegIFNα, pegylated interferon alfa; ULN, upper limit of normal; W, week.

- This pooled analysis included 131 patients who achieved undetectable[a] HDV RNA at EOT and had posttreatment data available from the MYR204 (NCT03852433) and MYR301 (NCT03852719) studies
- HDV RNA was determined using RoboGene 2.0 (lower limit of quantitation [LLOQ] = 50 IU/mL; limit of detection = 6 IU/mL)
  - Low viremic relapse was defined as any positive HDV RNA test result detected in the posttreatment period with all levels <50 IU/mL
  - High viremic relapse was defined as any posttreatment HDV RNA level ≥50 IU/mL
  - Sustained undetectable HDV RNA was defined as no positive HDV RNA test result throughout the posttreatment period

[a]Undetectable HDV RNA was defined as <LLOQ (50 IU/mL; target not detected).

Results

Patient Disposition



BLV, bulevirtide; EOT, end of treatment; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa; W, week.

- Of the 131 patients with undetectable HDV RNA at EOT included in the pooled analysis,
  - 57 (44%) had undetectable HDV RNA at all posttreatment visits
  - 14 (11%) had low viremic relapse with HDV RNA <50 IU/mL in the posttreatment period
  - 60 (46%) had high viremic relapse with HDV RNA ≥50 IU/mL in the posttreatment period

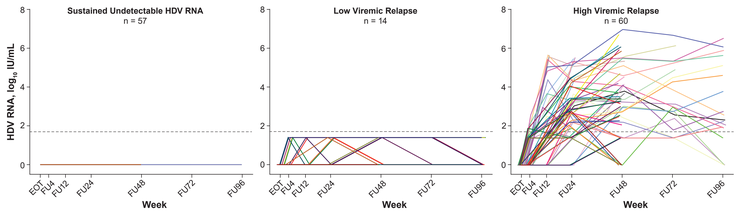
Demographics and Baseline Disease Characteristics

Patient Characteristics	Sustained Undetectable HDV RNA n = 57	Low Viremic Relapse n = 14	High Viremic Relapse n = 60
Age, years, mean (SD)	42.3 (8.9)	42.1 (10.7)	42.4 (7.5)
Sex, male, n (%)	40 (70)	10 (71)	29 (48)
Race, n (%)			
Asian	5 (9)	1 (7)	10 (17)
Black or African American	3 (5)	—	—
White	48 (84)	13 (93)	50 (83)
Other	1 (2)	—	—
BMI, kg/m^2, mean (SD)	25.4 (3.6)	25.0 (3.7)	25.6 (3.8)
Cirrhosis present, n (%)	20 (35)	5 (36)	20 (33)
Liver stiffness, kPa, mean (SD)	12.2 (7.5)	12.6 (6.8)	13.2 (7.8)
ALT, U/L, mean (SD)	106.1 (83.5)	117.1 (81.7)	95.3 (66.0)
HDV RNA, log$_{10}$ IU/mL, mean (SD)	4.2 (1.6)	4.3 (1.6)	5.2 (1.2)
Previous IFN therapy, n (%)	29 (51)	6 (43)	36 (60)
Concomitant HBV NA treatment, n (%)	30 (53)	7 (50)	33 (55)

ALT, alanine aminotransferase; BMI, body mass index; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; NA, nucleos(t)ide analogue.

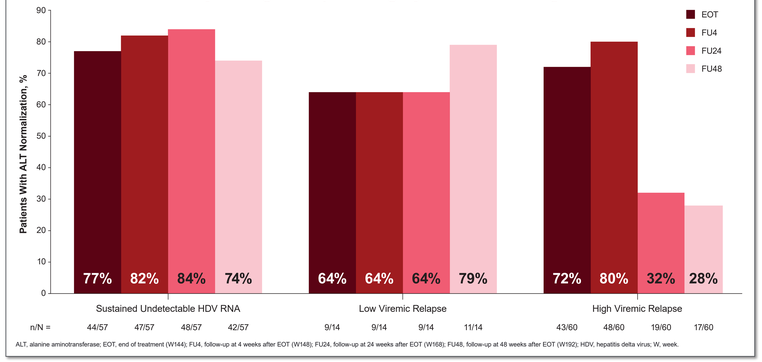
- Demographics and baseline characteristics were generally similar among patients with sustained undetectable HDV RNA and those with relapse in the posttreatment period
  - A smaller proportion of patients with high viremic relapse were male compared to those with sustained undetectable HDV RNA or low viremic relapse
  - Patients with high viremic relapse in the posttreatment period had higher mean baseline HDV RNA than those with sustained undetectable HDV RNA or low viremic relapse

HDV RNA by Virologic Relapse Category From EOT Through FU96



The dotted black line represents the LLOQ.
EOT, end of treatment (W144); FU4, follow-up at 4 weeks after EOT (W148); FU12, follow-up at 12 weeks after EOT (W156); FU24, follow-up at 24 weeks after EOT (W168); FU48, follow-up at 48 weeks after EOT (W192); FU72, follow-up at 72 weeks after EOT (W216); FU96, follow-up at 96 weeks after EOT (W240); HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; W, week.

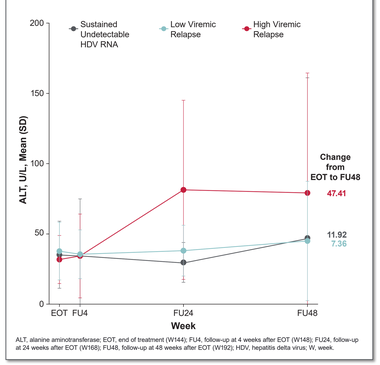
ALT Normalization Rate by Virologic Relapse Category From EOT Through FU48



ALT, alanine aminotransferase; EOT, end of treatment (W144); FU4, follow-up at 4 weeks after EOT (W148); FU24, follow-up at 24 weeks after EOT (W168); FU48, follow-up at 48 weeks after EOT (W192); HDV, hepatitis delta virus; W, week.

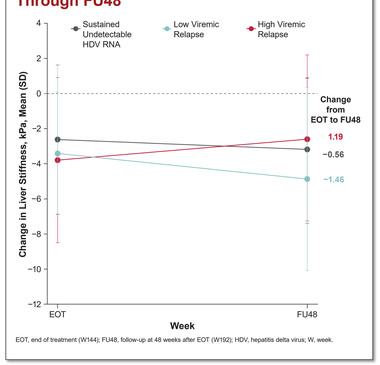
- Rates of ALT normalization were maintained in the posttreatment period in patients with sustained undetectable HDV RNA or with low viremic relapse
- In contrast, rates of ALT normalization in patients with high viremic relapse decreased over time in the posttreatment period

Mean ALT (U/L) by Virologic Relapse Category From EOT Through FU48



ALT, alanine aminotransferase; EOT, end of treatment (W144); FU4, follow-up at 4 weeks after EOT (W148); FU24, follow-up at 24 weeks after EOT (W168); FU48, follow-up at 48 weeks after EOT (W192); HDV, hepatitis delta virus; W, week.

Mean Change From Baseline in Liver Stiffness by Virologic Relapse Category From EOT Through FU48



EOT, end of treatment (W144); FU48, follow-up at 48 weeks after EOT (W192); HDV, hepatitis delta virus; W, week.

- Mean ALT levels at EOT were similar between patients who had sustained undetectable HDV RNA in the posttreatment period and those with relapse
- In patients with sustained undetectable HDV RNA and in those with low viremic relapse, mean ALT levels were stable throughout the posttreatment period
- In patients with high viremic relapse, mean ALT levels increased from 32 U/L at EOT to 81 U/L at follow-up at 24 weeks after EOT and remained elevated through follow-up at 48 weeks after EOT
- Mean liver stiffness decreased from baseline to EOT regardless of HDV RNA status, and continued to decline during the posttreatment period in the patients with sustained undetectable HDV RNA and low viremic relapse, but increased in patients with high viremic relapse