Compassionate use of REP 2139-Mg in HBV / HDV / HIV co-infection: a first Canadian experience

CASL STC 2023 Abstract 10

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Introduction

Chronic hepatitis delta (CHD) typically leads to cirrhosis and hepatic decompensation. REP 2139-Mg is a nucleic acid polymer (NAP) that blocks the assembly and secretion of HBV subviral particles and HDV ribonucleoprotein assembly and or HDV RNA replication (Figure 1), providing multiple effects against both HBV and HDV infection. Compassionate access to REP 2139-Mg is being provided under the Replicor Compassionate Access Program (RCAP, NCT05683548). Here we present the first interim analysis of the safety and efficacy of REP 2139-Mg in a Canadian cirrhotic patient with HBV / HDV / HIV co-infection.

Methods

The compassionate use of REP 2139-Mg was approved by Health Canada in a 53 year old Caucasian male with HBV/HDV/HIV co-infection (HDV genotype 1D) and cirrhosis (Child Pugh A5) with portal hypertension. Baseline fibroscan was 17.1 kPa (increased from 13 kPa in 2013). No HDV antiviral response was observed during a previous 1-year course of pegIFN in 2012. Under EVG/COB/FTC/TAF therapy, HBV and HIV infection were well controlled. The patient was negative for HBeAg and anti-HBeAg antibodies at baseline. Current antiviral therapy was supplemented with REP 2139-Mg (250mg SC QW) and pegIFN (90µg SC qW) for a planned duration of 48 weeks of therapy. HDV RNA was monitored using an in-house qRT-PCR (LLOQ 2750 copies/mL) with undetectable HDV RNA verified by nested PCR (National Microbiology Laboratory, Winnipeg, AB). HBsAg and anti-HBs were monitored by Abbott Architect quantitative platforms. HBV DNA and HIV RNA were monitored by Roche COBAS.

Results

Administration of REP 2139-Mg is accompanied by moderate but transient pain. PegIFN mediated decline in platelet count has stabilized at $78x10^9$/mL (Figure 2). No other adverse events have been observed.

Mild ALT elevation (57 U/L) initially normalized (25 U/L) and is currently 52 U/L. No alterations in liver synthetic function have been observed. At week 17, HDV RNA became undetectable (5.95 log_{10} copies/mL decline from baseline) and is currently < LLOQ at week 21. HBsAg has declined from 2348 to 1451 IU/mL. Baseline HIV RNA was 29 copies/mL but has remained undetectable at weeks 9, 17 and 21 of REP 2139-Mg therapy.

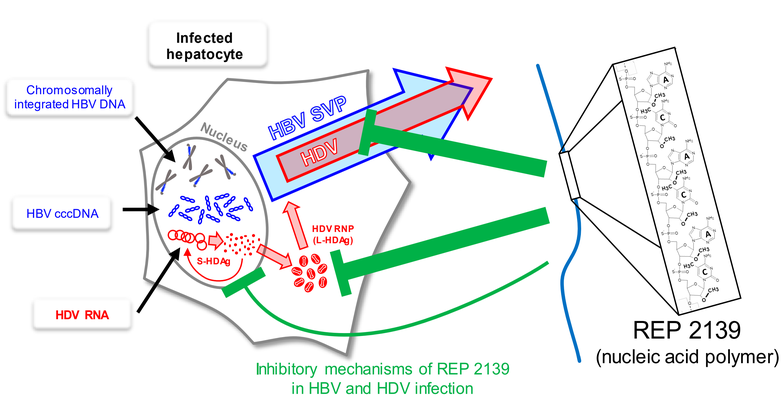

Figure 1.
Antiviral mechanisms of REP 2139 in HBV and HDV infection.
REP 2139-Mg blocks the assembly of HBV subviral particles and envelopment of the HDV ribonucleoprotein (RNP) via interaction with the HSP40 chaperone DNAJB12. Direct interaction with the small and large isoforms of HDAg results in inhibition of HDV RNA replication and or HDV RNP assembly.

Boulon et al., Hepatology 2021; 74: 512A, Vaillant, ACS Inf Dis 2019; 5: 675-687, Shamur et al., Hepatology 2017; 66: 504A

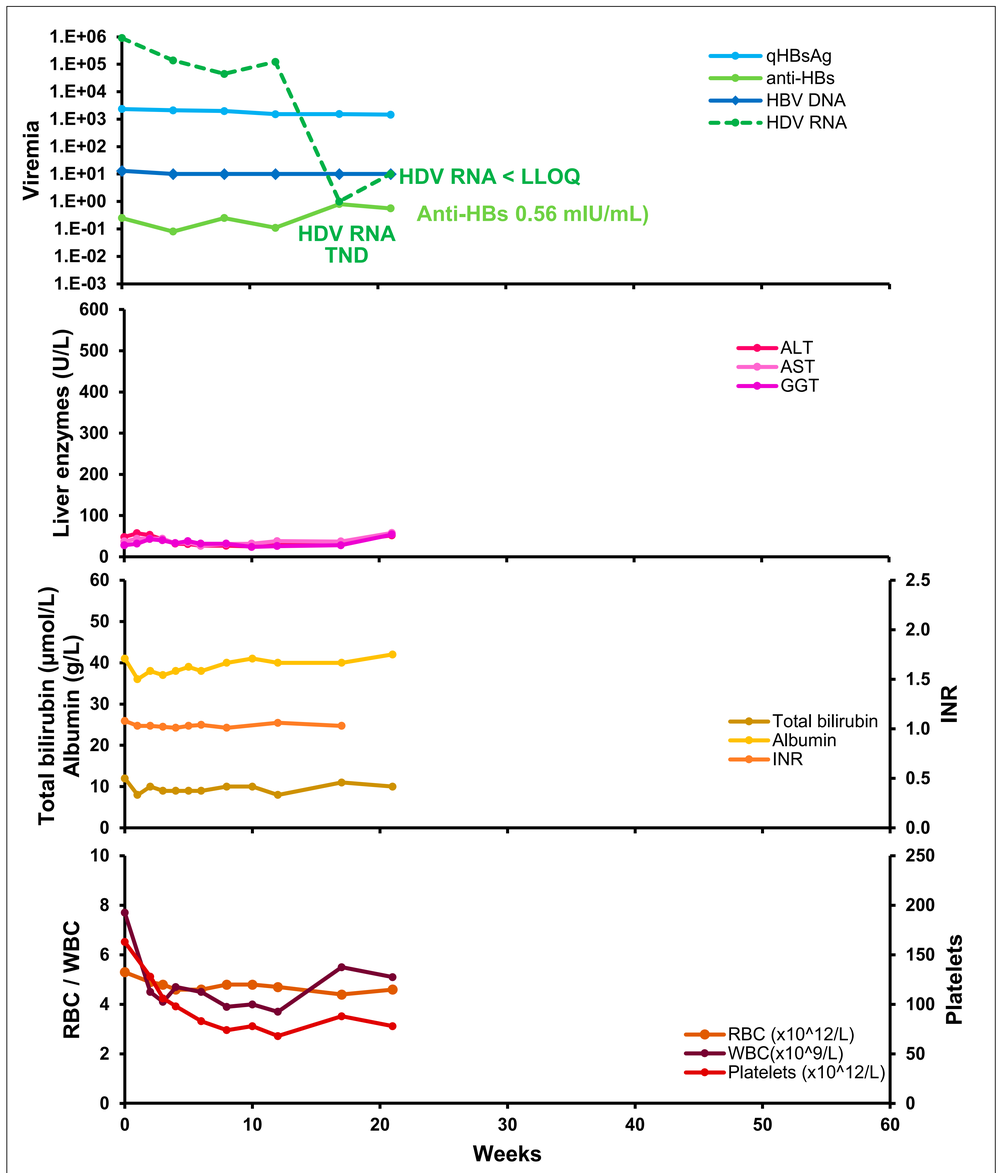

Figure 2. Responses to therapy.
Antiviral (top), liver enzyme (2nd from top), liver synthetic function (2nd from bottom) and hematological (bottom) responses to therapy with EVG/COB/FTC/TAF qD PO + 90µg qW SC pegIFN + 250mg qW SC REP 2139-Mg. qHBsAg and HBV DNA units are IU/mL, anti-HBs units are mIU/mL and HDV RNA units are copies/mL.

Conclusions

- **Subcutaneously administered REP 2139-Mg is safe and well tolerated in cirrhotic HBV / HDV / HIV co-infection.**
- **Early, strong decline of HDV RNA in this patient with delayed HBsAg response mirrors the antiviral responses observed in the previous phase IIA clinical trial with REP 2139-Ca (REP 301) and in recent compassionate use of REP 2139-Mg in cirrhotic bulevirtide failure patients and in decompensated cirrhosis.**
- **REP 2139-Mg use may be safe to expand to patients with HIV co-infection.**
- **REP 2139 (and phosphorothioate oligonucleotides in general) have no impact on CYP450 mediated metabolism. Efficacy of small molecule-based antiviral therapies against HBV and HIV do not appear to be impacted.**

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