Antiviral efficacy of REP 2139-Mg and effects on HVPG in HDV/HBV coinfected patients with cirrhosis and portal hypertension non-responding to previous bulevirtide treatment

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Introduction

The nucleic acid polymer (NAP) REP 2139-Mg demonstrated safety and antiviral efficacy in patients with hepatitis B/D virus (HBV/HDV) coinfection. We undertook to measure changes in hepatic venous pressure gradient (HVPG) accompanying antiviral response patients with HBV/HDV cirrhosis.

Method

REP 2139-Mg (250 mg SC qW) – available through a named patient use program (Replicor Compassionate Use Program, NCT05683548) – was administered for 48 weeks together with pegylated interferon (pegIFN, 90µg SC qW) and concomitant TAF or TDF therapy in 3 HDV/HBV patients, who failed previous bulevirtide therapy. All patients had cirrhosis and clinically significant portal hypertension (CSPH) and thus, also underwent HVPG measurement at baseline (BL), at week (W)12 and W48 (end of therapy, EOT).

Results

Patient 1 (Caucasian male, 69 y.o., Child-A5, large varices, HVPG 17mmHg) had BL HDV-RNA of 3.28 log10 copies/mL and quantitative HBs antigen (qHBsAg) 1202 IU/mL. By EOT, **no antiviral response** nor ALT flare was observed despite switching to weekly i.v. administration of REP 2139-Mg week 20 and dose increase to 500 mg by week 36, but qHBsAg decreased to 760 IU/mL. **HVPG** at W12 decreased to 14 mmHg (-18%) **returned to BL with 17mmH** (0% from BL) at EOT.

Patient 2 (Caucasian female, 51 y.o., Child-A5, large varices, HVPG 14mmHg) had BL HDV-RNA of 4.97 log10 copies/mL and qHBsAg of 626 IU/mL. The patient developed an ALT flare (max. 683 U/L, max. bilirubin 6.9 mg/dL) at W8, which was also seen with previous pegIFN exposure. After pegIFN discontinuation, ALT and bilirubin steadily declined during continued REP 2139-Mg therapy. **HDV-RNA was negative by week 16**. The patient was switched to IV administration by week 37. By EOT, HDV-RNA remained negative, **qHBsAg was at 0.5 IU/mL**, and ALT was normal at 28 U/L. **HVPG** increased to 17mmHg (+21%) at week 12 but **returned to 14 mmHg** (0% from BL) at EOT.

Patient 3 (Caucasian male, 38 y.o., Child-A5, large varices, HVPG 22mmHg) had a BL HDV-RNA of 4.52 log10 copies/mL and a qHBsAg of 922 IU/ml. After an initial ALT flare (max. ALT 659 U/L, bilirubin within normal range) at W7, **HDV-RNA was negative by week 27**. By EOT, HDV-RNA remained negative, **qHBsAg was at 0.18 IU/mL**, and ALT 41 U/L. **HVPG was 18 mmHg (-18%) at W12 and remained decreased to 19 mmHg (-14%) at EOT**.

REP 2139-Mg was well tolerated with no severe adverse events. SC injections were accompanied by local and transient grade 1 erythema and itching in patient 2. No adverse events were associated with IV infusion. In patient 2 and 3 antiviral clearance and normalization of transaminases was **stable at W60 (FU W12)**.

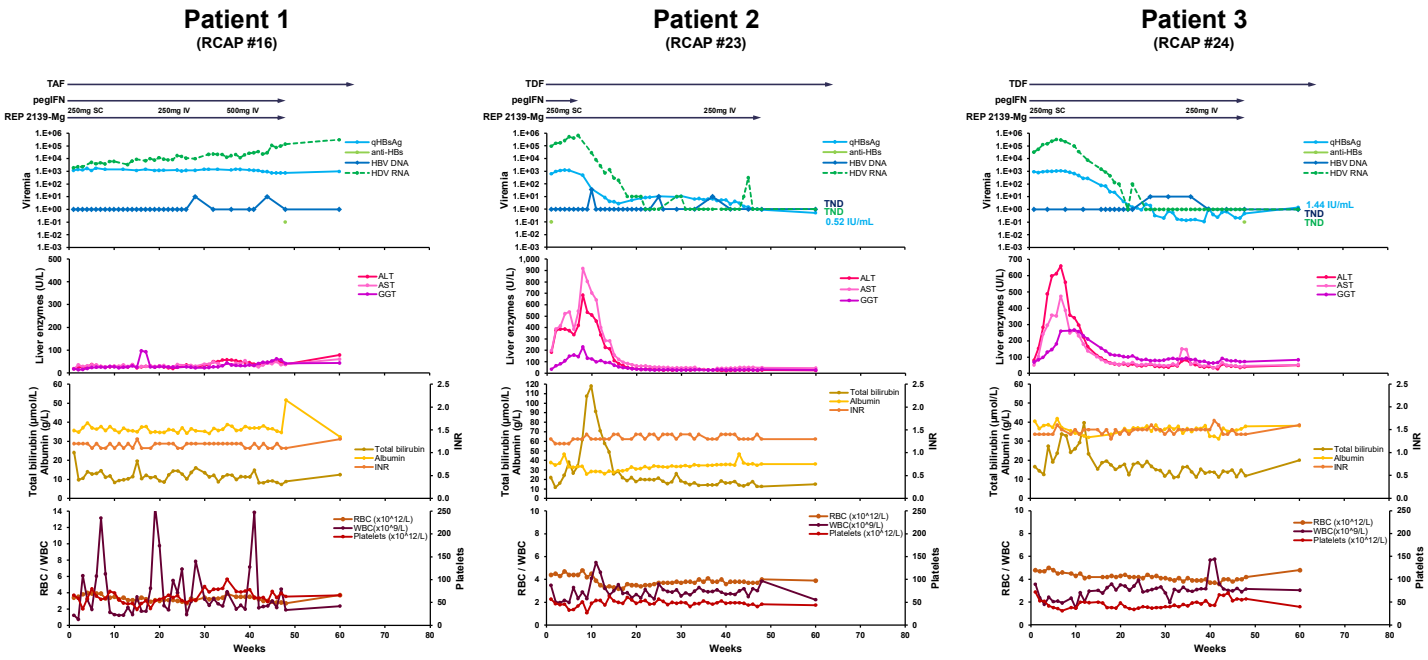

Figure 1. Antiviral and biochemical / hematological responses during REP 2139-Mg + pegIFN therapy in patients 1, 2 and 3.

Conclusions

Weekly REP 2139-Mg in combination with TDF and low-dose pegIFN appeared safe and effective against HBV/HDV infection in patients with cirrhosis and CSPH. **Two out of three patients achieved HDV RNA loss and HBsAg suppression**. Potential ALT flares should be monitored closely but may reflect an immune response triggering the subsequent decrease/loss of HDV-RNA and of HBsAg – as observed in our patients. Portal hypertension may remain controlled despite ALT flares during REP 2139-Mg therapy in patients with CSPH

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