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Abstract 1245

Safety and Efficacy of REP 2139-Mg-based Therapy in Austrian Patients with HBV / HDV Compensated Cirrhosis with Prior Failure to Bulevirtide

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INTRODUCTION

REP 2139-Mg is a nucleic acid polymer (NAP) with demonstrated safety and antiviral efficacy in patients with HBV/HDV coinfection. Three Austrian patients who failed to achieve virologic response to currently available treatments are currently being treated with Rep 2139-Mg provided for Named Patient Use.

REP 2139 inhibits HDV RNA replication and / or HDV RNP formation (see Poster 1461) via direct interaction with the small and large forms of HDAg and HDV envelopment and release by blocking the assembly of HBV subviral particles (Figure 1). The safety and efficacy of SC injection of REP 2139-Mg in combination therapy with pegylated interferon (PEG-IFN).

METHODS

REP 2139-Mg 250 mg s.c. qW and PEG-IFN 90 µg s.c. qW were added to TDF in three patients with compensated HBV/HDV-induced cirrhosis and clinically significant portal hypertension (CSPH) who failed to achieve negative HDV-RNA levels and/or virologic response to long-term BLV treatment (see Figure 2). Baseline characteristics are presented in Table 1. Safety/antiviral efficacy were evaluated weekly. Hepatic venous pressure gradient (HVPG) was measured at baseline and at week 12. Quantitative HBsAg and anti-HBs were measured by standard/commercially available assays, while HDV-RNA was quantified using an assay that was developed locally with a lower limit of detection of 100 cp/mL (convertible to IU/mL by division by 37).

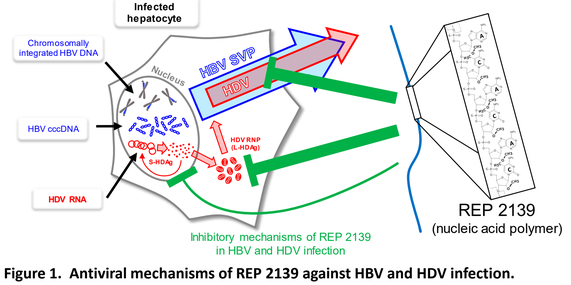

Figure 1. Antiviral mechanisms of REP 2139 against HBV and HDV infection.
REP 2139-Mg blocks the assembly of HBV subviral particles and envelopment of the HDV ribonucleoprotein (RNP) via interaction with the HSP40 chaperone DNAJB12. Direct interaction with the small and large isoforms of HDAg results in inhibition of HDV RNA replication and or HDV RNP assembly. Please see Fonte et al., Poster 1461.

Boulon et al., 2021; Hepatology 74: 512A
Shamur et al., 2017; Hepatology 66: 504A

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RESULTS

REP 2139-Mg was well tolerated with no related systemic adverse events. Injections were accompanied by grade 1 erythema and puritis in patient 2. Responses to therapy are indicated in Figure 3.

Patient 1 has not yet experienced an antiviral response at week 33 however, HVPG decreased by 18% (from 17 to 14 mmHg) at week 12. REP 2139-Mg therapy has now been transitioned to 500mg IV qW.

Patient 2 experienced an initial elevation of ALT (ALT_{max} 683 U/L) and bilirubin ($Bili_{max}$ 117 umol/L) with similar elevation as during previous PEG-IFN exposure. Upon halting pegIFN at week 7, ALT and bilirubin steadily declined during continued REP 2139-Mg therapy. HDV-RNA has declined to <LLOQ and HBsAg has declined to 10.92 IU/mL at week 30. However, HVPG increased at week 12 by 29% (from 14 to 18 mmHg), most likely related to the pegIFN-associated hepatitis flare.

Patient 3 experienced an initial ALT flare (ALT_{max} 659 U/L) with stable bilirubin and INR. At week 30, HDV-RNA has become undetectable and HBsAg has declined to 0.32 IU/mL. HVPG decreased at week 12 by 19% (from 22 to 18 mmHg).

Table 1. Patient baseline characteristics

Patient	1	2	3
Age (years)	69	51	38
Sex	Male	Female	Male
Ethnicity	Caucasian	Caucasian	Caucasian
ALT (U/L)	19	184	80
Total bilirubin (µmol/L)	24.11	21.89	16.59
Albumin (g/L)	35.6	37.6	40.5
Platelets (10^9/L)	66	57	72
INR	1.2	1.3	1.4
Child-Pugh	A5	A5	A5
Hepatic Venous Pressure Gradient (HVPG, mmHg)	17	14	22
HDV genotype	1	1	1
HDV RNA (IU/mL)	$1.9x10^3$	$9.3x10^4$	$3.3x10^4$
HBsAg (IU/mL)	1202.4	626	922
HBeAg status	Negative	Negative	Negative
HBV DNA (IU/mL)	Target not detected	Target not detected	Target not detected

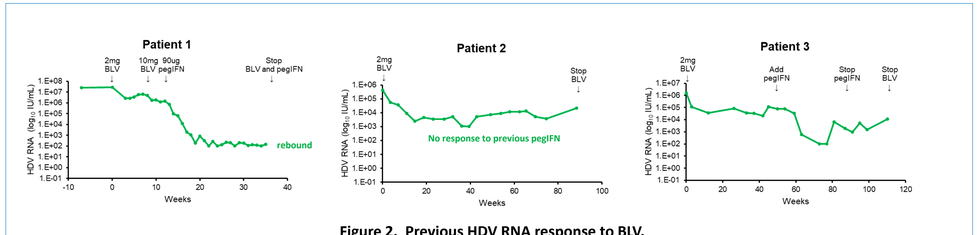

Figure 2. Previous HDV RNA response to BLV.

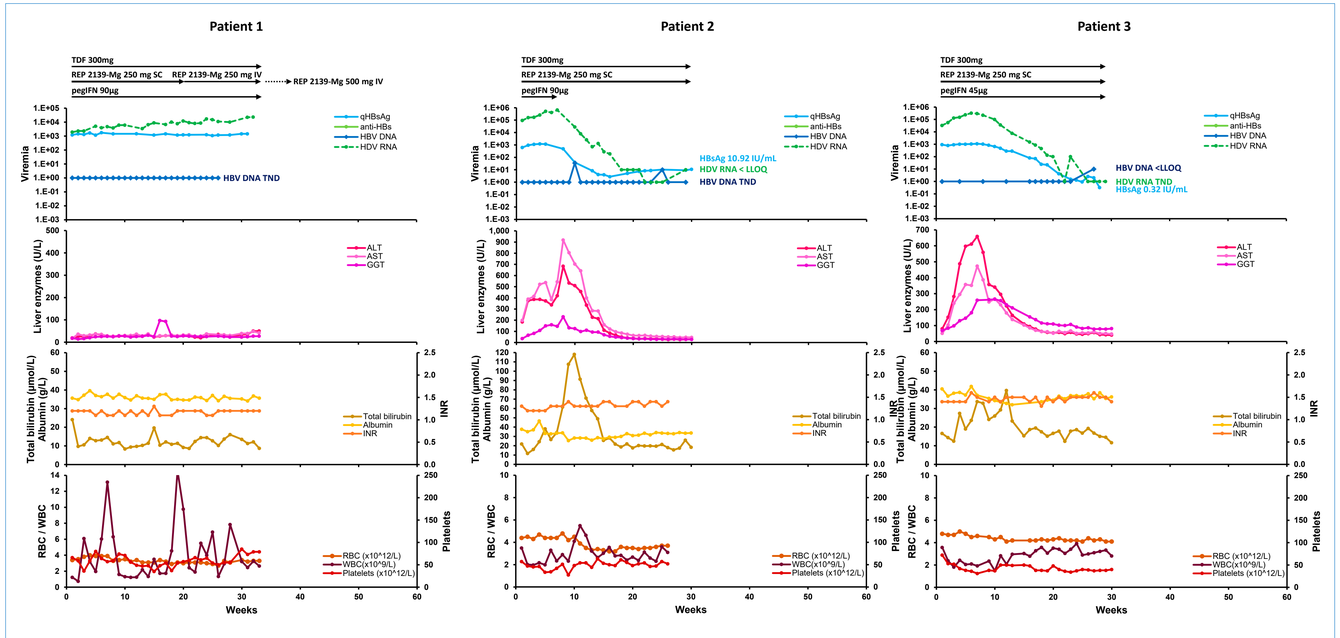

Figure 3. Response during REP 2139-Mg-based therapy

CONCLUSIONS

1. **Subcutaneous weekly REP 2139-Mg in combination with TDF and low-dose PEG-IFN appears safe and effective against HBV/HDV infection in three Austrian patients with compensated cirrhosis and CSPH.**
2. **The use of PEG-IFN in CSPH warrants close clinical/laboratory monitoring.**
3. **The reductions in HVPG observed in two patients suggest a clinically meaningful amelioration of portal hypertension that may translate into a decreased risk of hepatic decompensation.**
4. **Increased dose and/or switch to IV administration of REP 2139-Mg may be required to achieve antiviral response in some patients.**