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Abstract 1251

Safety and efficacy of REP 2139-Mg in association with TDF in chronic hepatitis delta patients with decompensated cirrhosis

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INTRODUCTION

- The only treatment option for chronic hepatitis delta (CHD) patients with decompensated cirrhosis is liver transplantation. There are no approved antiviral therapies for this special population.
- REP 2139 blocks HBV subviral particle assembly, HDV replication and morphogenesis (see poster 1461), driving HBsAg loss in CHD patients.
- REP2139 is safe and well tolerated in CHD patients with compensated disease (see poster 1246).

AIM

- The objective of this study is to describe the safety and efficacy of REP 2139-Mg in CHD patients with decompensated cirrhosis.

METHODS

- Compassionate access to REP2139-Mg has been approved by the ANSM in 3 CHD patients with decompensated cirrhosis (Replicor Compassionate Access Program, NCT05683548).
- Scheduled therapy is 48 weeks of REP 2139-Mg 250 mg QW SC and TDF 245 mg QD PO.
- Data were collected at baseline and every week for the first month, then every month.
- HBsAg and anti-HBsAg were determined using Abbott Alinity S (LLOD 0.02 and 0.0002 IU/mL respectively), HBV DNA using the Roche COBAS (LLOD 10 IU/mL), HDV RNA using the Eurobio EBX-004 assay (LLOD 100 IU/mL) and HBcrAg using the Fujirebio Lumipulse platform (LLOD 3log$_{10}$ U/ml).
- Intra-hepatic evaluation of HDV and HBV was performed in liver explants. Intracellular total HBV DNA and cccDNA was performed according to Allweiss *et al* using a QX200 BioRad droplet digital (dd)PCR approach. 3.5Kb RNA and intracellular HDV RNA were also quantitated by ddPCR after RQ1 DNase digestion. The housekeeping genes beta globin and GUSB were used as internal controls.

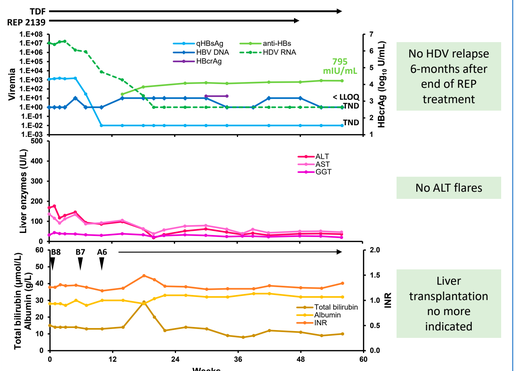
RESULTS

Table 1. Baseline characteristics

Patient	1 (RCAP 5)	2 (RCAP 8)	3 (RCAP 11)
Age (years)	56	56	47
Sex	Female	Female	Male
Ethnicity	Caucasian	African	African
ALT (U/L)	168	64	89
Total bilirubin (μmol/L)	15	44	24
Albumin (g/L)	28	24	24
Platelets (10^9/L)	56	90	35
INR	1.26	1.92	1.67
Child-Pugh / MELD	B8 / 9	C12 / 17	C10 / 13
HDV genotype	1	5	5
HDV RNA (IU/mL)	1.09x10^7	4285	34138
HBsAg (IU/mL)	1177	4270	1273
HBeAg status	Negative	Negative	Positive
HBV DNA (IU/mL)	TND	TND	< 10 IU/mL
Previous treatment	Naive	Relapse BLV	Naive

(TND = target not detected; BLV = bulevirtide)

Patient 1. Antiviral response and liver function



No HDV relapse 6-months after end of REP treatment

No ALT flares

Liver transplantation no more indicated

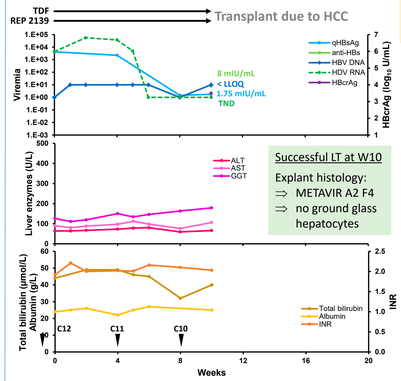
At baseline: Child-Pugh B8 with ascites and large EV

At W10: HBsAg loss

At W14: positive anti-HBs

- Ascites reversal since W4
- Compensated cirrhosis since W10
- Urinary sepsis at W18 => no liver decompensation

Patient 2. Antiviral response and liver function



Successful LT at W10

Explant histology:
⇒ METAVIR A2 F4
⇒ no ground glass hepatocytes

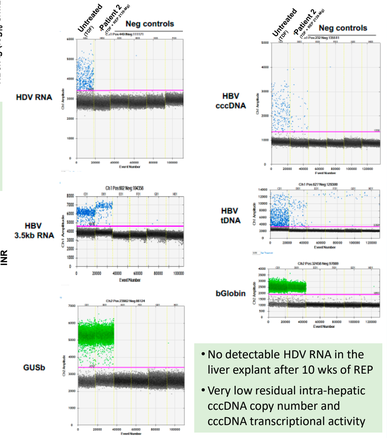
At baseline: Child-Pugh C12 with ascites and HCC

At W6: HDV-RNA TND

At W10: HBsAg 1.75 IU/mL

- Ascites reversal since W4
- Child B9/C10 at W10 (LT)

Intrahepatic analysis of replicative markers of HDV and HBV infection



- No detectable HDV RNA in the liver explant after 10 wks of REP
- Very low residual intra-hepatic cccDNA copy number and cccDNA transcriptional activity

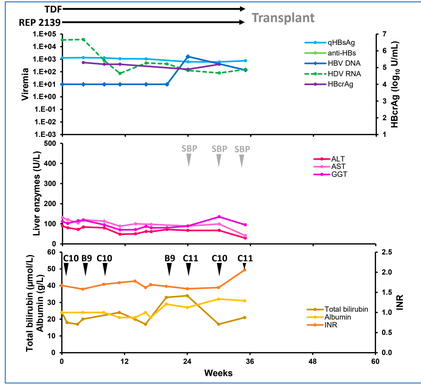
Table 2. Intrahepatic assessment of HBV and HDV replication

	Untreated explant (TDF)	Patient 2 (TDF + REP 2139-Mg)
HBV cccDNA (copies/bGlobin)	0.004	0.002
HBV tDNA (copies/bGlobin)	0.01	0.005
HBV 3.5Kb RNA (copies/GUSB)	0.002	0.00005
3.5Kb RNA/cccDNA	0.5	0.025
HDV RNA (copies/GUSB)	0.02	0

CONCLUSIONS

1. **REP 2139-Mg is safe and well tolerated in CHD patients with decompensated cirrhosis.**
2. **REP 2139-Mg can clear HDV RNA from the blood and liver.**
3. **HBV-HDV functional cure appears achievable for the first time in this special population, which could prevent the need for liver transplant.**

Patient 3. Antiviral response and liver function



At baseline: Child-Pugh C10 with previous history of variceal bleeding, chylous ascites (since 2021) and hepatic encephalopathy

At W11: HDV-RNA 2.7 log IU/mL decline

Albumin IV perfusion QW after paracentesis due to relapse of chylous ascites may be sequestering REP 2139 Gaus et al, Nuc Acids Res 2019

Successful liver transplantation (LT) at W35

Explant histology: METAVIR A0 F4
=> no ground glass hepatocytes

- SC administration of REP 2139-Mg has been well tolerated.
- No significant AE (including ALT elevation) have been observed to date.

CONTACT

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