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Abstract 1223

Compassionate use of subcutaneously administered REP 2139-Mg in cirrhotic HBV / HDV co-infection

Marc Bourlière[1], Veronique Loustaud-Ratti[2], Christiane Stern[3], Michel Bazinet[4], Souad Ben Ali[1], Laurence Lecomte[1], Sandrine Francois[2], Cecilia de Freitas[3], Athenaïs Gerber[5], Ségolène Brichler[5], Emmanuel Gordien[5], Andrew Vaillant[4]

1. Service Hépato-Gastro-Entérologie, Hôpital Saint-Joseph, Marseille, France, 2. Department Hepatogastroenterology, Centre hospitalier universitaire à Limoges, Limoges, France, 3. Department de Hépatologie, AP-HP Hôpital Beaujon, Clichy, France
4. Replicor Inc. Montreal, Canada, 5. Centre national de référence des hépatite B, C et Delta – Laboratoire associé, Hôpital Avicenne, Bobigny, France

INTRODUCTION

REP 2139 inhibits HDV RNA replication and HDV RNP formation via direct interaction with the small and large forms of HBsAg and HDV envelopment and release by blocking the assembly of HBV subviral particles (Figure 1). The chelate complex formulation of NAPs (REP 2139-Mg) neutralizes subcutaneous (SC) administration reactivity. The safety and efficacy of SC injection of REP 2139-Mg in combination therapy is currently being assessed in cirrhotic patients with chronic HBV / HDV co-infection who fail to respond to bulevirtide (BLV) or where use of BLV is contraindicated.

METHODS

Compassionate use of REP 2139-Mg therapy was approved by L'Agence nationale de sécurité du médicament et des produits de santé. Patients either had established chronic HBV / HDV co-infection with compensated cirrhosis who failed to respond or rebounded on BLV or with decompensated cirrhosis. TDF therapy was supplemented with 90µg pegIFN qW and 250mg REP 2139-Mg qW via SC administration. PegIFN was not used with decompensated cirrhosis. Safety assessments included liver, kidney and hematological function. Virologic assessments included HDV RNA (Robogene MK II / Eurobiotec), HBV DNA (Abbott), HBsAg and anti-HBs (Abbott Architect quantitative). A pan genotypic nested RT-PCR was used to verify antiviral response in non genotype 1 HDV patients. Undetectable HBV DNA / HDV RNA was right censored to 1 IU/mL, undetectable HBsAg was right censored to 0.01 IU/mL, HBsAg < 10 mIU/mL was left censored to 2 mIU/mL. Data in this presentation are up to date as of October 27, 2022.

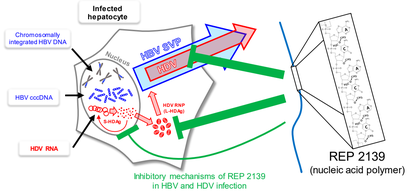


Figure 1. Antiviral mechanisms of REP 2139 against HBV and HDV infection.

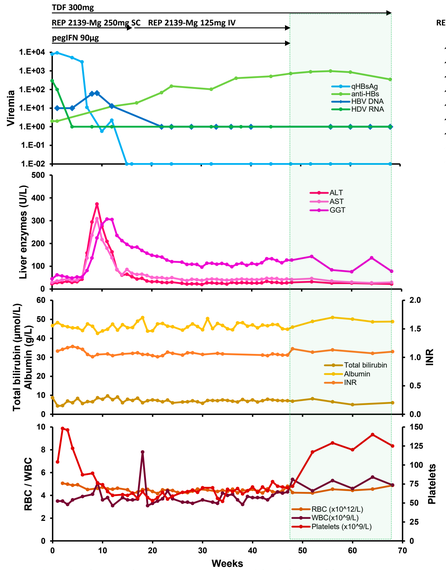
REP 2139-Mg blocks the assembly of HBV subviral particles and envelopment of the HDV ribonucleoprotein (RNP) via interaction with the HSP40 chaperone DNAJB12. Direct interaction with the small and large isoforms of HDAg results in inhibition of HDV RNA replication and or HDV RNP assembly.

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

RESULTS

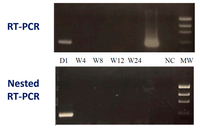
Patient 1: Senegalese male, 51
Chronic HBV/HDV (GT5)
Compensated cirrhosis

Previous treatment failure:
TDF + pegIFN
TDF + pegIFN + 2mg BLV



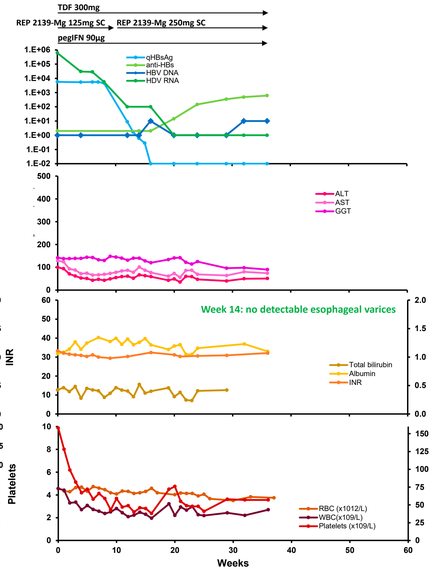
Sustained HBsAg loss, seroconversion, with undetectable HDV RNA and normal ALT for 20 weeks in the absence of REP 2139-Mg and pegIFN

Pan-genotypic HDV RT-PCR confirming HDV RNA response in Patient 1



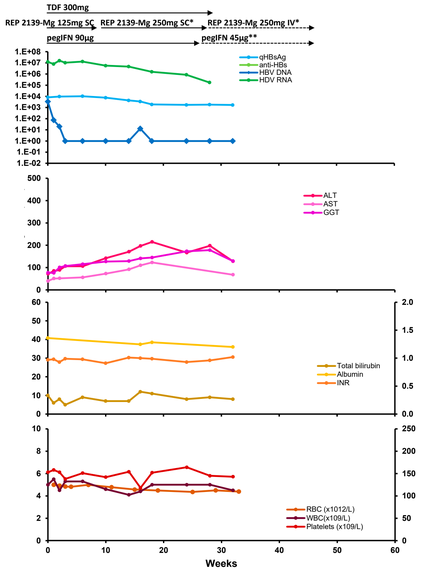
Patient 2: Caucasian male, 47
Chronic HBV/HDV (GT1)
Compensated cirrhosis
Child A5, stage 1 esophageal varices

Previous treatment failure:
TDF + pegIFN
TDF + pegIFN + 2mg BLV



Patient 3: Asian male, 54
Chronic HBV/HDV (GT1)
Compensated cirrhosis, central obesity

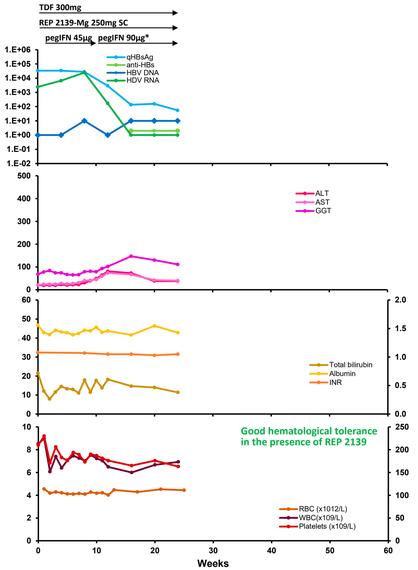
Previous treatment failure:
TDF + pegIFN
TDF + pegIFN + 2mg BLV
TDF + pegIFN + 10mg BLV



*High BMI likely compromising liver targeting via SC administration
** Transition to 45µg pegIFN due to lip lesions.

Patient 4: Caucasian female, 59
Chronic HBV/HDV (GT1)
Compensated cirrhosis

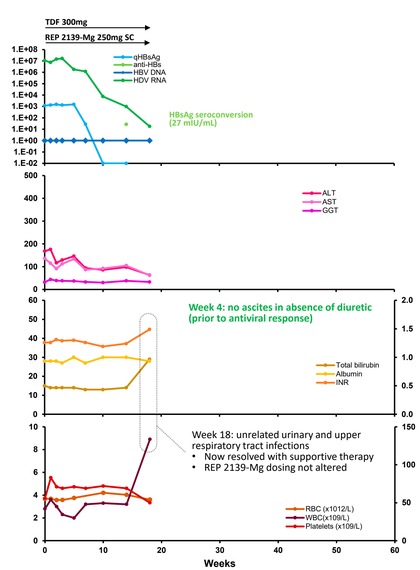
Previous treatment failure:
TDF + pegIFN (hematological intolerance)
TDF + 2mg BLV
TDF + 10mg BLV



***PegIFN tolerability significantly improved in the presence of REP 2139**

Patient 5: Caucasian female, 54
Chronic HBV/HDV (GT1)
Decompensated cirrhosis with significant ascites

PegIFN and BLV therapy contraindicated in this patient



ADVERSE EVENTS

Patient 4 experiences mild persistent erythema and transient pain following SC injections. These AE do not prevent adherence to SC therapy.

Liver enzyme elevations are otherwise asymptomatic (host mediated) in all patients.

No other drug-related adverse events to date.

CONCLUSIONS

1. **The magnesium chelate formulation of REP 2139 effectively suppresses the serious injection site reactivity commonly observed with subcutaneously administered oligonucleotides.**
2. **SC REP 2139-Mg and associated liver enzyme flares are safe and well tolerated in these cases of compensated and decompensated cirrhosis.**
3. **SC REP 2139-Mg (in combination with TDF and pegIFN) is accompanied by identical virologic responses as observed with its intravenous infusion:**
   - **Rapid HBsAg loss and seroconversion**
   - **Rapid clearance of serum HDV RNA**
   - **Host mediated transaminase flares suggesting clearance of HBV infected hepatocytes from the liver.**
4. **Reduced dosing of pegIFN (90ug) may be sufficient to synergize with REP 2139 to restore immune function.**
5. **Improved pegIFN tolerability and rapid reversal of ascites prior to antiviral response suggest additional hepatoprotective effects of REP 2139-Mg.**

CONTACT

Marc Bourlière: mbourliere@hopital-saint-joseph.fr

Andrew Vaillant: availlant@replicor.com