AASLD The Liver Meeting® Nov. 10-14, 2023

Abstract 1246

Safety and efficacy of REP 2139-Mg-based therapy in French patients with prior failure to pegIFN and or bulevirtide

Marc Bourlière[1], Veronique Loustaud-Ratti[2], Christiane Stern[3], Souad Ben Ali[1], Edouard Bardou-Jacquet[4], Laurent Alric[5], Lea Colombain[6], Magdalena Meszaros[7], Jose Ursic Bedoya[7] Sophie Metivier[8], Philippe Mathurin[9], Michel Bazinet[10], Laurence Lecomte[1], Sandrine Francois[2], Cecilia de Frietas[3], Anita Levacher[4], Christopher Morvan[6], Ségolène Brichler[11], Athenaïs Gerber[11], Emmanuel Gordien[11] Stéphane Chevaliez[12], Andrew Vaillant[10]

1. Service Hépato-Gastro-Entérologie, Hôpital Saint-Joseph, Marseille, France, 2. Service d'Hépato-Gastroentérologie, CHU de Limoges, Limoges, France, 3. Service d'Hépatologie, AP-HP Hôpital Beaujon, Clichy, France, 4. Service des Maladie du Foie, CHU de Rennes, Rennes, France, 5. Service de médecine interne-maladies digestives, CHU Rangueil, Université Toulouse 3, Toulouse, France, 6. Centre Hospitalier de Perpignan, Perpignan, France, 7. CHU Montpelier, Montpellier, France, 8. Service d'hepatologie, CHU Rangueil, Université Toulouse 3, Toulouse, France, 9. Service des Maladies de l'appareil digestif et nutrition – Hépatologie, CHRU de Lille, Lille, France, 10. Replicor Inc. Montreal, Canada, 11. Centre national de référence des hépatite B, C et Delta – Laboratoire associé, Hôpital Avicenne, Bobigny, France, 12. Service de Virologie, Hôpital Henri Mondor, Créteil, France

INTRODUCTION

REP 2139 blocks HBV subviral particle assembly and hepatitis delta antigen function (see poster 1461), driving HBsAg loss in HBV infection and HBsAg / HDV RNA loss in HBV / HDV co-infection. Compassionate access to REP 2139-Mg is being provided under the Replicor Compassionate Access Program (RCAP, NCT05683548). The safety and efficacy of weekly SC injection of REP 2139-Mg in combination therapy is currently being assessed in cirrhotic patients with chronic HBV / HDV co-infection after failure on pegIFN and or bulevirtide (BLV).

METHODS

Compassionate access to REP 2139-Mg has been approved by the ANSM in 15 patients (See Table 1) with compensated cirrhosis at baseline who had either no response or viral escape of HDV RNA during 2 or 10mg BLV. Existing TDF was supplemented with 48 weeks of QW SC 250mg REP 2139-Mg and 90 µg pegIFN. Weekly safety evaluations were accompanied by virologic assessment every 4 weeks. HBsAg and anti-HBsAg were determined using Abbott Architect or Alinity S platforms, HBV DNA was assessed using the Roche COBAS platform, HDV RNA was assessed using the Eurobio EBX-004 assay and HBcrAg was assessed using the Fujirebio Lumipulse platform.

Table 1. Patient baseline characteristics

Parameter	Mean (where applicable) (range)
Number	**15**
Age	**48.25** (21-59)
Sex	**7 female, 8 male**
Ethnicity	**9 Caucasian, 4 African, 1 Asian, 1 Central Asian**
Previous failure to pegIFN	**12**
BLV failure type	**Non response (< 2 log_{10} decline): 5** **HDV RNA rebound during therapy: 10**
Liver status	**11 Compensated cirrhosis** (CP A5: 7, CP A6: 3, 1 unknown) **2 Fibrosis F3** **2 Fibrosis F4**
HBeAg status at baseline	**12 negative, 3 positive**
HDV genotype (Done centrally at Hôpital Avicenne)	**10 genotype 1** **2 genotype 5** **1 genotype 7** 2 genotypes to be assessed
HIV co-infection	**1**
HDV RNA (IU/mL)	**3.17 x10^6** (295-1.68x10^7)
HBsAg (IU/mL)	**11178** (2200-33559)
HBV DNA (IU/mL)	**281** (TND-3440)
ALT (U/L)	**97.2** (20-266)
Bilirubin (µmol/L)	**14.9** (8-34)

RESULTS

At least 8 weeks of REP 2139-Mg therapy have been completed in all 15 patients. Extension of therapy > 48 weeks is currently underway in two patients (see Figure 1).

REP 2139-Mg administration has been well tolerated, with transient grade 1 erythema. An ALT flare > 5X baseline occurred in 1 patient. ALT has normalized 7/8 patients with HDV RNA decline > 2 log_{10} IU/mL from baseline at week 25-48 of therapy. No liver decompensation or REP 2139-Mg related AEs have been observed. Transition to IV infusion occurred in 1 patient at week 2 due to poor SC tolerability and in 4 patients (at weeks 19-24) to improve the speed of antiviral response. Three patients did not receive pegIFN and 2/3 experienced stable depression in platelet counts (≤ grade 1). Platelet declines (grade 1-3) occurred in all 12 patients receiving pegIFN. PegIFN therapy was removed in one patient at week 56 (anemia), another at week 4 (tolerability) and a third at week 8 (petechial hemorrhages), all self-resolving with continued REP 2139-Mg exposure.

Withdrawal of REP 2139-Mg + pegIFN has occurred in two patients (Figure 1). Undetectable HDV RNA and HBsAg and HBsAg seroconversion have been stable after withdrawal of REP 2139-Mg and pegIFN for 10 and 6 months. One of these patients has now had TDF withdrawn with HBV DNA remaining additionally undetectable for 6 months (functional cure).

HDV RNA and HBsAg response (> 50% decline from baseline) is currently observed in 12/15 patients. Additional details are presented in Table 2. In the 9 patients with > 24 weeks of therapy, 7 have > 2 log_{10} decline in HDV RNA (all with normal ALT) with 5 having undetectable HDV RNA. Of these 5 patients, 3 have undetectable HBsAg and 2 have anti-HBs seroconversion. An additional patient under extension therapy (who became HDV RNA undetectable at week 20) has now achieved undetectable HBsAg at week 68 of therapy (see Figure 2). Early strong HDV RNA and HBsAg declines are observed in the patient with HBV / HDV / HIV with HIV viral load remaining undetectable (Figure 3). HBeAg loss with anti-HBe seroconversion has occurred in 2/3 patients HBeAg positive at baseline.

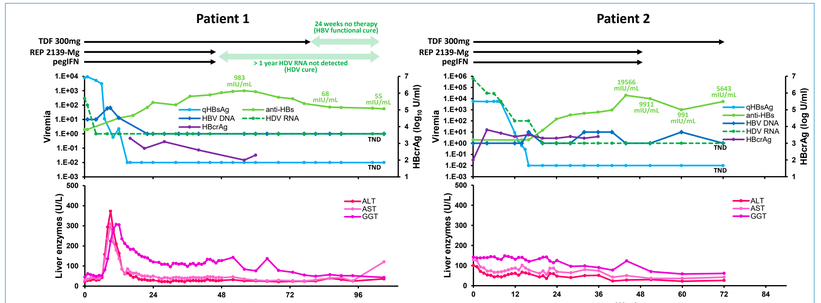

Figure 1. Antiviral response in patients completing therapy.

Table 2. Virologic response during therapy

Virologic response	Duration of therapy							
	1-4 weeks (n=15)	5-8 weeks (n=15)	9-12 weeks (n=14)	13-24 weeks (n=12)	25-48 weeks (n=10)	> 48 weeks (n=2)*	Removal of NAP + pegIFN (n=2)	Removal of TDF (n=1)
Any HDV RNA decline from baseline	5	8	9	8	8	2	2	1
HDV RNA ≥ 2 log_{10} decline from baseline	3	6	8	7	8	2	2	1
HDV RNA < LLOQ	2	4	4	6	6	2	2	1
HDV RNA target not detected	1	1	2	6	6	1	2	1
Any HBsAg decline from baseline	1	3	6	7	8	2	2	1
HBsAg > 1 log_{10} decline from baseline		1	4	6	6	2	2	1
HBsAg > 2 log_{10} decline from baseline		1	3	5	5	2	2	1
HBsAg < 10 IU/mL			2	3	5	2	2	1
HBsAg < 0.05 IU/mL				2	3	1	2	1
Anti-HBs seroconversion			1	2	2	1	2	1
ALT normal				3	7	1		

* One patient with HDV RNA TND (Week 20) but clearance of HBsAg had not occurred at 48 weeks, HBsAg loss occurred at week 68.
One patient with increased dosing with > 2 log_{10} decline of HDV RNA with detectable HBsAg at week 48. HDV RNA loss occurred with HBsAg XXX at week 71.

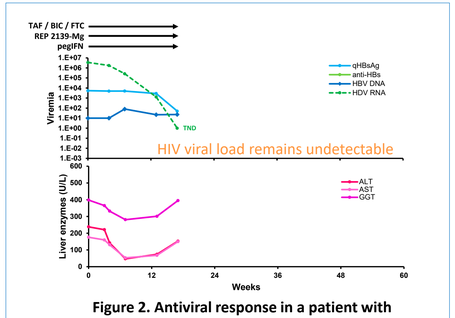

Figure 2. Antiviral response in a patient with HBV / HDV / HIV co-infection.

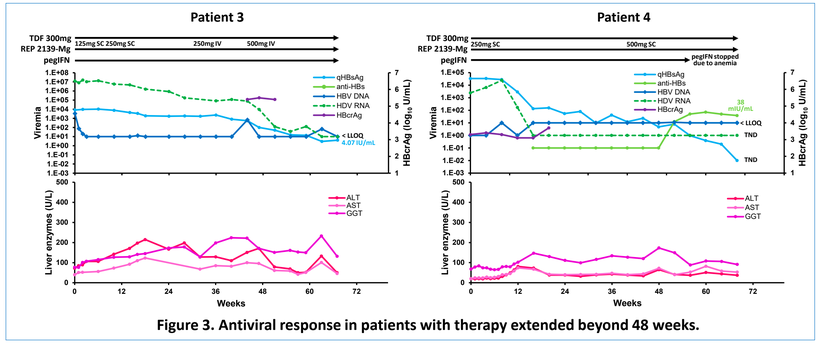

Figure 3. Antiviral response in patients with therapy extended beyond 48 weeks.

CONCLUSIONS

1. **Subcutaneous REP 2139-Mg is safe, and effective against HBV and HDV infection in combination with TDF and low dose pegIFN in patients with compensated cirrhosis.**
2. **REP 2139-Mg can achieve HDV cure and functional cure of HBV in this patient population.**
3. **REP 2139-Mg can salvage poor HDV virologic response to BLV or HDV viral rebound during BLV therapy.**
4. **REP 2139-Mg is effective against HBV and HDV infection in the presence of HIV co-infection.**

CONTACT

Marc Bourliere: mbourlière@hopital-saint-joseph.fr

Andrew Vaillant: availlant@replicor.com