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Interferon free clearance of HDV RNA and HBsAg seroconversion in a cirrhotic subject with chronic HBV / HDV co-infection with TDF and REP 2165-Mg

Adrian Streinu-Cercel[1,2], Michel Bazinet[3], Carina Elsner[4], Ulf Dittmer[4], Hedwig Roggendorf[5], Michael Roggendorf[5], Andrew Vaillant[3]

1. National Institute of Infectious Diseases "Prof. Dr. Matei Bals" Bucharest, 2. Romania, Carola Davila University of Medicine and Pharmacy, Bucharest, Romania
3. Replicor Inc. Montreal, Canada, 4. Institute for Virology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, 5. Technical University of Munich, Munich, Germany

INTRODUCTION

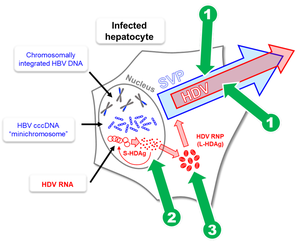
REP 2139 and REP 2165 are nucleic acid polymers (NAPs) which block the assembly / secretion of HBV subviral particles, reduce intracellular HBsAg[1,2] to clear intrahepatic HBsAg *in vivo*[3] and additionally bind to the small and large forms of HDAg[4], driving multiple antiviral mechanisms against HDV infection (see Fig. 1)[5]. In HBV infection, the antiviral effects of NAPs are mediated by their interaction with DNAJB12, a HSP40 chaperone involved in the assembly of spherical SVP (LP42). In the previous REP 301[6] and REP 401[7] studies, combination therapy with NAPs and pegIFN in HBV/HDV co-infection was well tolerated and achieved HBsAg clearance and seroconversion and functional cure of HDV (HDV RNA target not detected, normal ALT) and functional cure of HBV (HBV DNA target not detected, HBsAg < 0.05 IU/mL, normal ALT) in a high proportion of participants. The magnesium chelate complex of REP 2165 (REP 2165-Mg) has similar asymptomatic administration and potent antiviral effect as REP 2139-Mg in HBV infection but with reduced accumulation in organs and blood. Interferon-free therapy with TDF and REP 2165-Mg is currently being assessed in a compassionate use cirrhotic subject with HBV / HDV co-infection.

Figure 1. Antiviral effects of REP 2165:

(1) Inhibition of HBV SVP assembly / secretion and HDV envelopment.

(2) Potential inhibition of HDV RNA synthesis via interaction with S-HDAg.

(3) Potential inhibition of HDV RNP formation via interaction with L-HDAg.



MATERIALS & METHODS

Compassionate use was approved by the Romanian Health Authority. The subject (male, 59 years of age) had confirmed HBV / HDV co-infection since April 2016. Advanced cirrhosis and portal hypertension were confirmed by ultrasound, fibroscan (35.3 kPa) and abnormal liver tests (ALT 360 U/L, GGT 320 U/L, bilirubin 4.7 mg/dL, INR 2.28 and platelets $60x10^3$/ uL).

Following written informed consent, therapy was started on Jan 15, 2019 with daily TDF (300mg) and once weekly IV REP 2165-Mg, given for 2 weeks at 125mg then increased to 250mg thereafter. Infusion of REP 2165-Mg in normal saline has transitioned from 250cc/2h to 100cc/1h.

Following saturation of weak HBsAg seroconversion, vaccination with Sci-B-Vac™ is currently underway using an accelerated double dose protocol previously established[8].

Local safety and efficacy assessments in Romania are being supplemented by confirmation of antiviral response to therapy using standard assays in Essen, Germany: HBV DNA (Abbott Realtime), HDV RNA (Robogene MKII) and quantitative HBsAg and anti-HBs (Abbott Architect).

VIROLOGIC, BIOCHEMICAL AND HEMATOLOGICAL RESPONSE

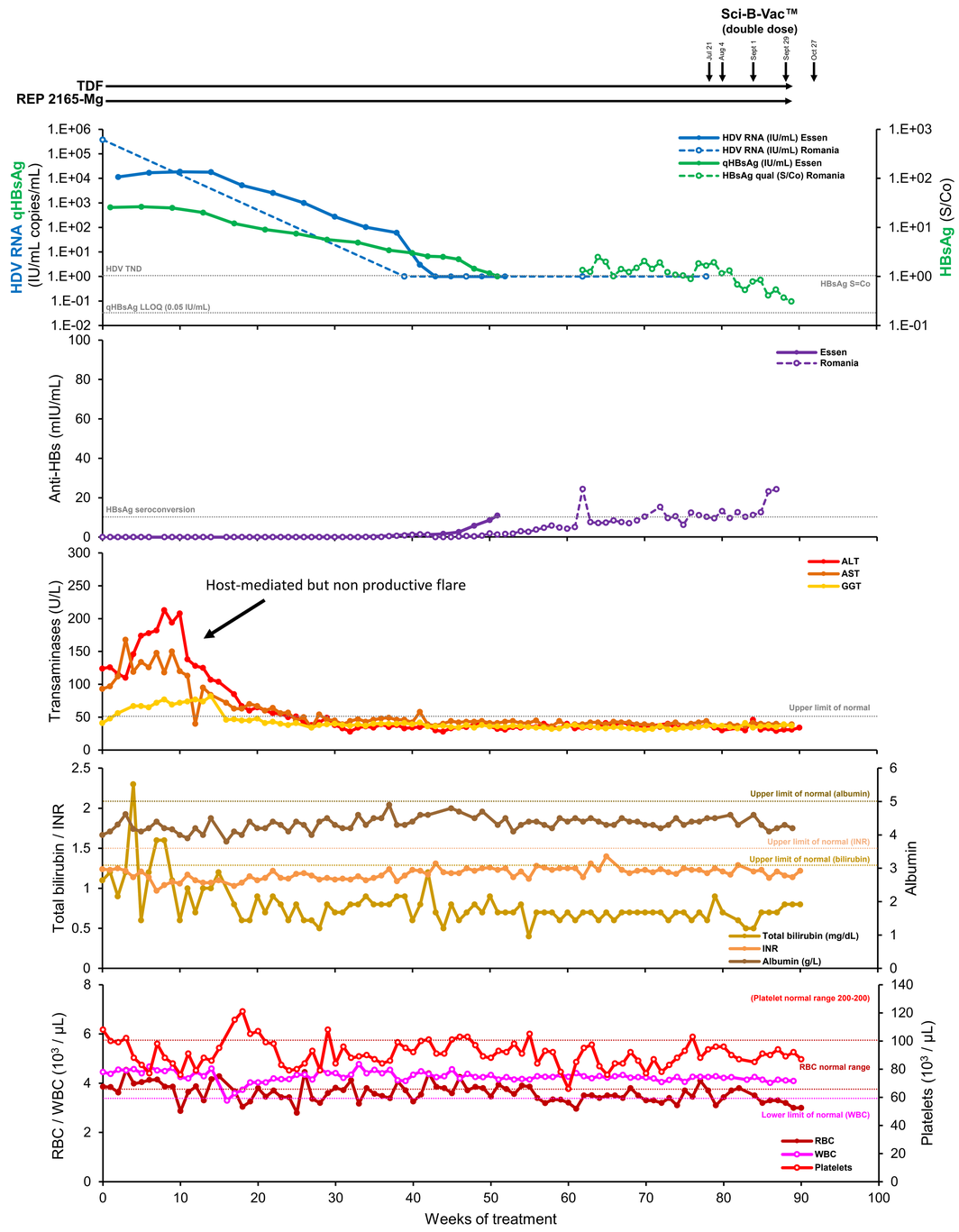


Figure 2. HBV / HDV antiviral responses during therapy.
Serial responses in virology, HBsAg seroconversion, serum transaminases, liver function and hematology are presented.

ADVERSE EVENTS

Administration of REP 2165-Mg has been asymptomatic to date.

No drug related AEs have been observed.

Unrelated viral pneumonia at week 9 resolved with supportive therapy with no alteration in dosing.

Burst esophageal varices at week 15 self resolved with supportive therapy. REP 2165-Mg was withheld on week 15 only as a precautionary measure and then resumed the following week.

Hematological parameters have remained stable to date with no supportive therapy.

CONCLUSIONS

1. **TDF combined with REP 2165-Mg is well tolerated with chronic exposure in this cirrhotic patient.**
2. **Early mild transaminase flare was asymptomatic and followed by clearance of HDV RNA and HBsAg reduction to 1.01 IU/mL (currently negative on the qualitative HBsAg platform).**
3. **This flare is likely non-productive due to its weak nature and the presence of HBsAg. Flares associated with functional cure of HBV are typically associated with ALT_{max} of > 400 U/L and HBsAg of < 1 IU/mL.**
4. **Therapeutic vaccination with Sci-B-Vac has shown no increase in anti-HBs after three double doses.**
5. **The relatively slow response with REP 2165 in this HBV/HDV co-infected participant versus REP 2139 monotherapy[6] suggests that the greater liver accumulation with REP 2139 may be associated with stronger antiviral effect against HDV.**
6. **Establishment of functional cure of HBV with NAPs and pegIFN was accompanied by strong host mediated flares in the absence of HBsAg and strong seroconversion[6,7]. The absence of both these milestones in this patient indicates the need for immunotherapy to achieve functional cure of HBV.**

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DISCLOSURES

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Contact information: astreinucercel@yahoo.com
availlant@replicor.com