Compassionate use of REP 2165-Mg in chronic HBV/HDV patients with progressive liver disease and failure to previous pegIFN therapy

Gheorghe Placinta[1], Victor Pântea[1], Lilia Cojuhari[1], Valentin Cebotarescu[1], Michel Bazinet[2], Andrew Vaillant[2]

1. Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Moldova, 2. Replicor Inc., Montreal, Canada

Contact information
availlant@replicor.com

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Introduction

REP 2165 is an analog of REP 2139 no longer in development with identical activity to REP 2139 in HBV and HDV in clinical studies (achieving HBV functional cure and HDV cure)[1,2] but with weaker liver accumulation due to increased sensitivity to endonuclease cleavage[2]. The remaining REP 2165-Mg drug product from the REP 401 study[1] is being deployed to meet international demand for compassionate access to NAP therapy.

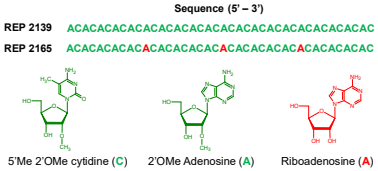
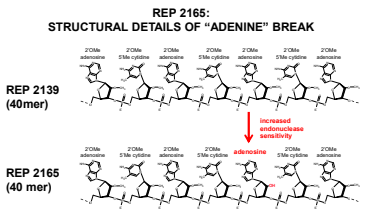


Figure 1. REP 2139 vs REP 2165 structure



Adenine breaks in REP 2165 permit degradation to 10mers (1/2 life 48 hours) allowing more rapid clearance from organs

Figure 2. REP 2165 degradation mechanism.

Method

Prior to REP 2165-Mg treatment, two chronic HBV/HDV Caucasian patients (1: female 46 y.o. and 2: male 51 y.o.) with rapid progression of liver disease (F3 fibrosis) received therapy with pegIFN (patient 1) or TDF + pegIFN (patient 2). Patient 1 completed 48 weeks of pegIFN with HDV RNA TND (no HBsAg response) but with HDV rebound after removal of pegIFN. After 50 weeks of TDF + pegIFN, patient 2 had only achieved a 1 log decline in HDV RNA (no HBsAg response).

REP 2165-Mg was initially dosed at 500mg once weekly by intravenous infusion. Patient 1 received REP 2165-Mg + pegIFN. Existing TDF + pegIFN therapy in patient 2 was supplemented with REP 2165-Mg. Therapy was scheduled for 48 weeks. Safety and biochemical response were monitored weekly and virologic response every 4 weeks using standard assays for quantitative HBsAg (LLOQ 0.05 IU/mL) and anti-HBs (cutoff for seroconversion 10 mIU/mL), HBV DNA (LLOQ 10 IU/mL) and HDV RNA (LLOQ 10 IU/mL).

Results

Patients 1 and 2 have completed 50 and 48 weeks of combination therapy. IV infusion of REP 2165-Mg in both patients was accompanied by fever and chills requiring supportive therapy for the first 4 weeks. REP 2165-Mg dosing was reduced to 250mg QW in both patients after week 12 due to rapid elimination of HDV RNA and initial strong initial HBsAg response. REP 2165-Mg dosing was increased back to 500mg at week 22 in patient 1 due to suboptimal HBsAg response. NAP therapy continues in this patient until compassionate supply is exhausted. REP 2165-<MG + pegIFN administration since week 4 was asymptomatic with no supportive therapy and no other AEs have been observed. Patient 1 has experienced several discrete ALT flares during therapy (3x baseline) and patient 2 experienced ALT elevation starting at week 7 and persisting at 3x baseline from week 12 to week 24. ALT normalized in patient 2 by end of therapy (week 48). ALT flares were otherwise asymptomatic with no changes in liver synthetic function.

Patient 1 achieved HDV RNA loss persistent since week 12. Initial HBsAg decline saturated at approximately 1.79 log from baseline (during dose reduction to 250mg). Following return to 500mg dosing, HBsAg decline continued is currently 7.7 IU/mL at week 48 (3.04 log decline from baseline). Anti-HBs seroconversion has persisted since week 16 (currently 42 IU/mL).

Patient 2 achieved HDV RNA loss persistent since week 8. HBsAg < 0.05 IU/mL was achieved at week 40. Anti-HBs seroconversion has persisted prior to week 12 (currently 1312 mIU/mL). Following week 48, all therapy (including TDF) has been removed from this patient.

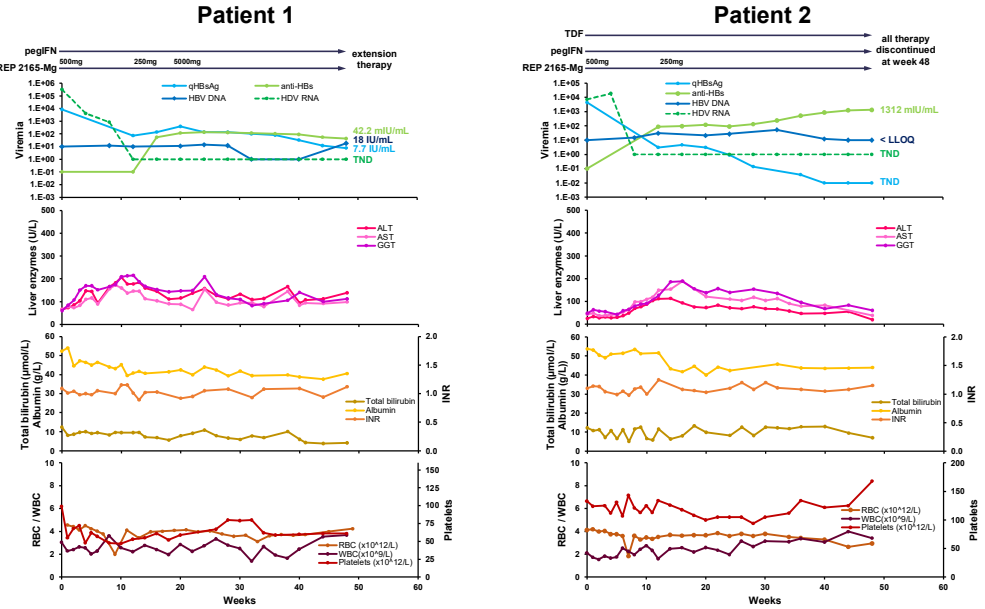


Figure 3. Antiviral and biochemical / hematological responses during REP 2165-Mg therapy in patients 1 and 2.

Conclusions

Although REP 2165-Mg is no longer in clinical development, it demonstrates excellent safety and efficacy against HBV and HDV infection in patients with advanced liver disease with prior pegIFN failure. These results confirm previous clinical data with REP 2139-Mg and REP 2165-Mg and expand the database of NAP compassionate use. These results will contribute to the design of upcoming phase IIA studies.

References

Bazinet et al., Gastroenterology 2020; 158: 2180-2194
Roehl et al., Molecular Therapy Nucleic Acids 2017; 8: 1-12