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Establishment of High Rates of Functional Cure of HBeAg Negative Chronic HBV Infection with REP 2139-Mg Based Combination Therapy: Ongoing Follow-up Results from the REP 401 Study

M. Bazinet[1], V. Pântea[2], G. Placinta[2], I. Moscalu[3], V. Cebotarescu[2], L. Cojuhari[2], P. Jimbei[4], L. Iarovoi[2], V. Smesnoi[4], T. Musteata[4], A. Jucov[2,3], A. Krawczyk[5] A. Vaillant[1]

1. Replicor Inc. Montreal, Canada, 2. Department of Infectious Diseases, Nicolae Testemitanu State University of Medicine and Pharmacy, Chișinău, Republic of Moldova
3. ARENSIA Exploratory Medicine, Republican Clinical Hospital, Chișinău, Republic of Moldova, 4. Toma Ciorbă Infectious Clinical Hospital, Chișinău, Republic of Moldova., 5. Universitätsklinikum Essen, Institute for Virology, Essen, Germany.

replicor
Infectious Disease Clinic Toma Ciorbă Hospital
Universitätsklinikum Essen

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INTRODUCTION

Circulating HBsAg blocks immune control of HBV infection and > 99.99% is synthesized and secreted independently from viral replication as subviral particles (SVP). REP 2139 blocks the assembly and subsequent release of all SVP[1], allowing the efficient clearance of serum HBsAg. This clearance facilitates the restoration of functional control of HBV infection by immunotherapy in HBV and HBV / HDV-co-infection[1,2]. The REP 401 protocol (NCT02565719) is a randomized, controlled trial assessing the safety and efficacy of REP 2139 and a derivative with enhanced tissue clearance REP 2165 in combination with tenofovir disoproxil fumarate (TDF) and pegylated interferon alfa-2a (peg-IFN) in patients with chronic HBeAg negative HBV infection.

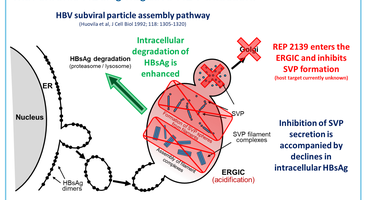

Figure 1. Antiviral mechanism of REP 2139 in HBV infection.

METHODS

Twenty four weeks of lead-in TDF (300mg PO qD) was followed by randomization (1:1) into experimental and control groups (Table 1). The experimental group received 48 weeks of TDF (300mg PO qD), peg-IFN (180ug SC qW) and REP 2139-Mg or REP 2165-Mg (1:1, 250 mg IV infusion qW) (Table 2). The control group was to receive 48 weeks of TDF + peg-IFN but all patients have crossed over to 48 weeks of experimental therapy in the absence of a 3 log drop in HBsAg after 24 weeks of peg-IFN (see figure below). Viremia is monitored on the Abbott Architect and Realtime platforms.

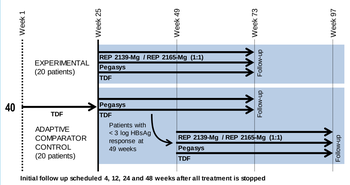

Figure 2. Design of REP 401 study.

Table 1. REP 401 Baseline Characteristics

Parameter		Adaptive comparator control (TDF + pegIFN)	Experimental (TDF + pegIFN + NAPs)
Age (average / median)		36.9 / 36	38.6 / 39.5
Sex		27M / 3F	26M / 4F
HBV genotype	A	1	2
	D	19	18
Metavir score (based on Fibroscan)	F0-F1	12	10
	F2	4	7
	F2-F3	0	2
	F3-F4	4	1
Virologic baseline (average / median)	HBV DNA (IU/mL)	$3.6x10^7$ / $8.7x10^8$	$4.8x10^6$ / $4.8x10^8$
	HBsAg (IU/mL	14775.7 / 9302.5	9018.1 / 8743
	Anti-HBs (mIU/mL)	0.78 / 0.1	2.778 / 0.1
ALT (U/L, average / median)		71.65 / 49	91.95 / 56.5

DISCLOSURES

MB and AV are employees and shareholders in Replicor Inc.

CONTACT

availlant@replicor.com

RESULTS

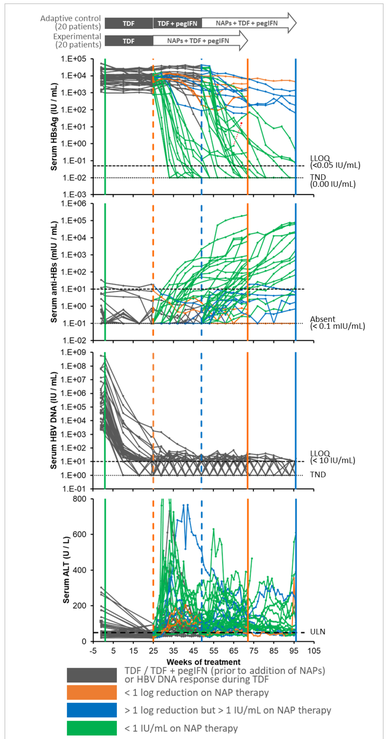

Figure 3. On-treatment responses in the REP 401 study.
Responses to REP 2139-Mg and REP 2165-Mg were indistinguishable. Global individual patient responses are presented for HBsAg, anti-HBs, HBV DNA and ALT and are color-coded according to HBsAg response (see legend above) for HBsAg, anti-HBs and ALT. The red HBsAg segment indicates off-treatment rebound in a single REP 2165 adaptive control patient who entered early into follow-up due to pegIFN related depression.

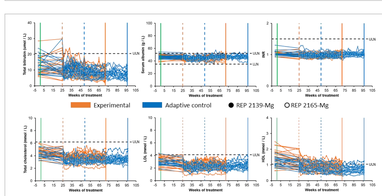

Figure 4. Liver function in the REP 401 study.
Globally normal bilirubin, albumin and INR (top row) and lipid dynamics (bottom row) indicate liver metabolic and synthetic function was normal during all ALT elevations observed.

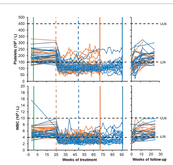

Figure 5. Management of pegIFN-induced hematological changes
PegIFN-induced hematological changes were indistinguishable in the presence or absence of NAPs. Global changes in WBC and platelets during treatment and follow-up are provided (see legend in Figure 4). Mild to moderate changes in WBC and platelets was otherwise asymptomatic and effectively managed with pegIFN dose reduction and / or eltrombopag without affecting antiviral response and recovered to baseline during follow-up.

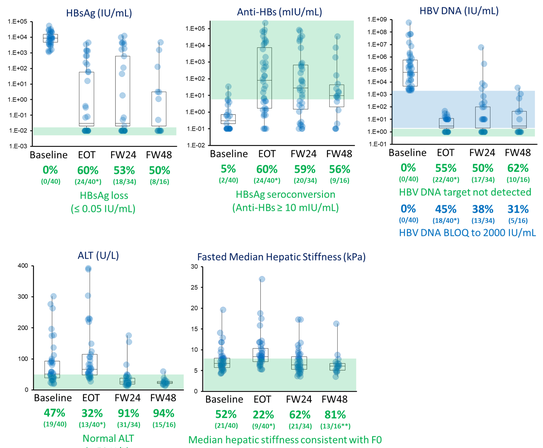

Figure 6. High rates of functional control and normalization of liver function persist after therapy in the REP 401 study.
Population analysis at baseline, end of treatment and during follow-up are presented for HBsAg (top left), anti-HBs (top middle), HBV DNA (top right), serum ALT (bottom left) and fasted median hepatic stiffness (bottom right) are presented. High rates of HBsAg loss, HBsAg seroconversion, undetectable HBV DNA, normal ALT and continual reduction in median hepatic stiffness are chronically persistent after removal of therapy. Summary results are presented in Table 2.

Table 2. REP 401 Treatment and Follow-up Summary

Patients entered into trial		**40**
End of treatment HBsAg response	> 1 log from baseline	36 (90%)
	< 1 IU/mL	**27 (67%)**
	≤ 0.05 IU/mL	**24 (60%)**
Patients currently completed treatment and 24 - 48 weeks of follow-up		**34**
Stable, inactive HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)		15 (44%)
Functional cure (HBsAg and HBV DNA target not detected)		14 (41%)
Therapy not indicated (AASLD / EASL guidelines) Clinical benefit (Low risk of fibrosis progression and HCC)		**29 (85%)**

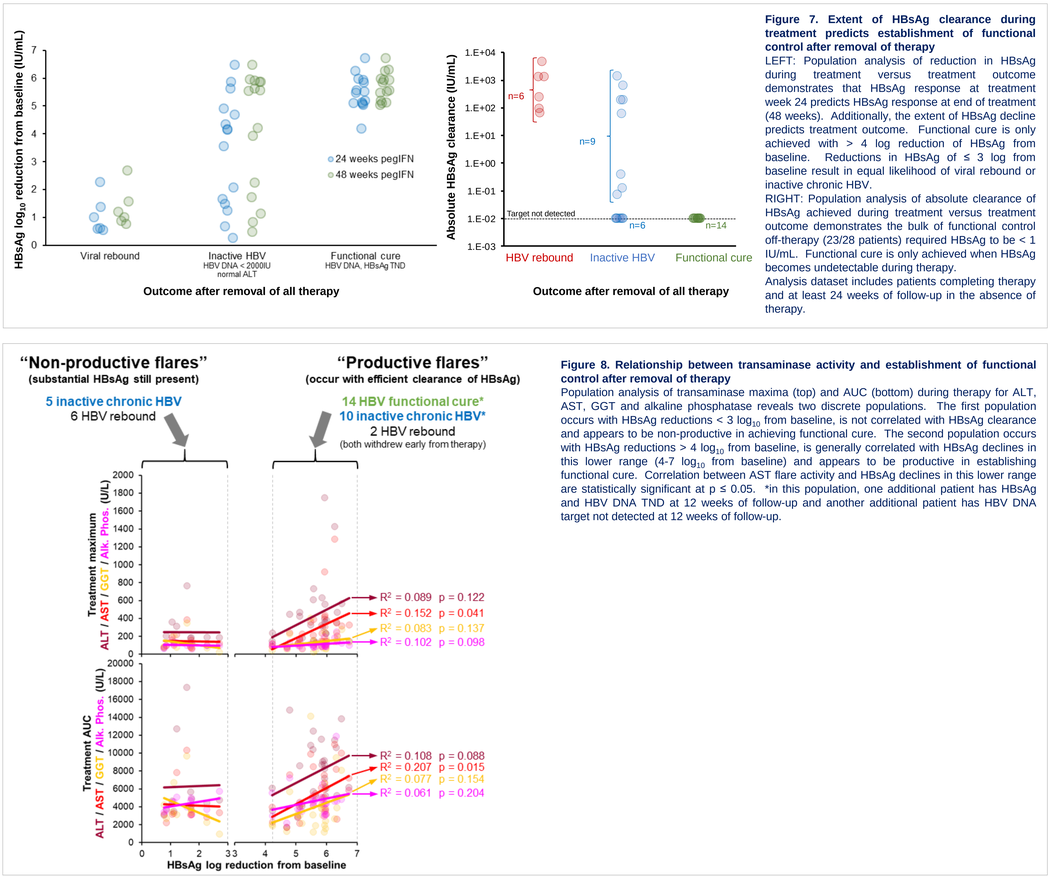

Figure 7. Extent of HBsAg clearance during treatment predicts establishment of functional control after removal of therapy
LEFT: Population analysis of reduction in HBsAg during treatment versus treatment outcome demonstrates that HBsAg response at treatment week 24 predicts HBsAg response at end of treatment (48 weeks). Additionally, the extent of HBsAg decline predicts treatment outcome. Functional cure is only achieved with > 4 log reduction of HBsAg from baseline. Reductions in HBsAg of ≤ 3 log from baseline result in equal likelihood of viral rebound or inactive chronic HBV.
RIGHT: Population analysis of absolute clearance of HBsAg achieved during treatment versus treatment outcome demonstrates the bulk of functional control off-therapy (23/28 patients) required HBsAg to be < 1 IU/mL. Functional cure is only achieved when HBsAg becomes undetectable during therapy.
Analysis dataset includes patients completing therapy and at least 24 weeks of follow-up in the absence of therapy.

Figure 8. Relationship between transaminase activity and establishment of functional control after removal of therapy
Population analysis of transaminase maxima (top) and AUC (bottom) during therapy for ALT, AST, GGT and alkaline phosphatase reveals two discrete populations. The first population occurs with HBsAg reductions < 3 $\log_{10}$ from baseline, is not correlated with HBsAg clearance and appears to be non-productive in achieving functional cure. The second population occurs with HBsAg reductions > 4 $\log_{10}$ from baseline, is generally correlated with HBsAg declines in this lower range (4-7 $\log_{10}$ from baseline) and appears to be productive in establishing functional cure. Correlation between AST flare activity and HBsAg declines in this lower range are statistically significant at $p \leq 0.05$. *in this population, one additional patient has HBsAg and HBV DNA TND at 12 weeks of follow-up and another additional patient has HBV DNA target not detected at 12 weeks of follow-up.

CONCLUSIONS

1. Inhibition of subviral particle assembly by REP 2139 leads to intracellular declines of HBsAg, inhibition of release of HBsAg derived from cccDNA and integrated HBV DNA and allows efficient clearance of HBsAg during therapy.
2. When REP 2139-Mg is combined with pegylated interferon over 48 weeks, functional control no longer requiring therapy (inactive chronic HBV or functional cure) is achieved in at least 85% of patients completing therapy.
3. Functional control of HBV infection is accompanied by normalization of liver function and reversal of fibrosis (as measured by Fibroscan).
4. Outcome of therapy may be predicted by HBsAg response after 24 weeks of therapy.
5. Establishment of functional control in the majority (23/28) of patients requires HBsAg clearance to < 1 IU/mL (typically > 4 $\log_{10}$ reduction from baseline).
6. Establishment of functional cure requires elimination of detectable HBsAg from the blood (0.00 IU/mL) during therapy.
7. Transaminase flares appear to be immune mediated and are not associated with any signs of liver toxicity in patients with fibrosis from F1 to F4 (as measured by Fibroscan). ***See poster P03-01 for additional detail.***
8. "Productive" transaminase flares occur with HBsAg declines > 4 $\log_{10}$ from baseline, are generally correlated with HBsAg declines > 4 $\log_{10}$ (typically < 1IU/mL) and are correlated with the establishment of functional cure.

REFERENCES

1. Blanchet et al., Antiviral Research 2019; in press
2. Bazinet et al., Lancet Gastroenterol & Hepatol. 2017; 2:877-889.
3. Al-Mahtab et al, PloS One 2016; 11: e0156667.

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