Nucleic acid polymer REP2139 monotherapy reveals a short half-life of serum HBsAg in HBeAg+ chronically infected HBV patients

N. Borochov[1], S.J. Cotler[1], S.L. Uprichard[1], M. Al-Mahtab[2], M. Bazinet[3], A. Vaillant[3], H. Dahari[1]

1. The Program for Experimental & Theoretical Modeling (PETM), Division of Hepatology, Department of Medicine, Loyola University Chicago, Maywood, IL, United States
2. Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
3. Replicor Inc., Montreal, Quebec, Canada

EASL The Home of Hepatology
THE INTERNATIONAL LIVER CONGRESS™ 2017
19-23 APRIL, AMSTERDAM, THE NETHERLANDS

INTRODUCTION

- Previous efforts to estimate the half-life ($t_{1/2}$) of serum HBsAg were confounded by slow or absent HBsAg decline during therapy.
- Nucleic acid polymers (NAPs) are a new class of antiviral that significantly reduce circulating HBsAg by blocking its release from infected hepatocytes (**Fig. 1**) and therefore provide a unique opportunity to estimate HBsAg $t_{1/2}$ and study HBV-host dynamics.

AIM

To characterize HBV DNA and HBsAg inhibition kinetics during monotherapy with REP2139 in the REP 102 protocol (NCT02646189).

METHODS

- HBeAg positive patients with confirmed chronic infection were enrolled in the REP 102 protocol who were treatment naive, non-cirrhotic with baseline ALT < 5X ULN.
- Twelve HBeAg+ chronically infected HBV patients were given weekly 500mg IV infusions of REP 2139 for 20-40 weeks [1].
- HBsAg and anti-HBs levels were measured weekly using quantitative Abbott Architect® assays.
- HBV DNA levels were measured biweekly using the Roche Cobas® assay.
- Segmented liner regression analyses were performed using R 3.2.0.

RESULTS

- Mean baseline viral load (VL) and HBsAg were 7.9±1.3 log cp/ml and 4.5±0.7 log IU/ml, respectively. All patients had anti-HBs<10 mIU/ml. Three patients with no decline in VL or HBsAg were excluded (not shown).
- VL remained at baseline 0-14 weeks before 3 patients (**Fig. 2A**) had a monophasic decline ($t_{1/2}$=11.2±6.4 d) and 6 patients had a biphasic decline consisting of a 12.0±2.6 wk 1st phase ($t_{1/2}$=5.3±1.5 d) followed by a 2nd phase plateau (n=1; **Fig. 2B**) or slower decline ($t_{1/2}$=5.0±2.3 wk ; **Fig. 2C**).
- HBsAg kinetic patterns were more complex. After a 0-16 week delay (**Fig. 2**), HBsAg decline was monophasic (n=3, **Fig. 2A**), biphasic (n=1; not shown), triphasic (n=3, **Fig. 2C**) or staircase (n=2, **Fig. 2B**).
  a) Monophasic HBsAg decline was 0.53±0.25 log/wk ($t_{1/2}$=5.0±3.0 d).
  b) Biphasic HBsAg decline exhibited a rapid phase (0.56 log/wk; $t_{1/2}$=3.8 d) followed by a slower phase (0.09 log/wk; $t_{1/2}$=24 d).
  c) The mean 1st phase decline in the triphasic and staircase cases was 0.53±0.26 log/wk ($t_{1/2}$=5.4±3.4 d), followed by complex kinetic patterns.
- Anti-HBs appearance in 6 patients (>10 mIU/ml) was not associated with VL or HBsAg inhibition patterns (**Fig. 2**). One patient (**Fig. 2C**) had extremely rapid increase in anti-HBs levels.

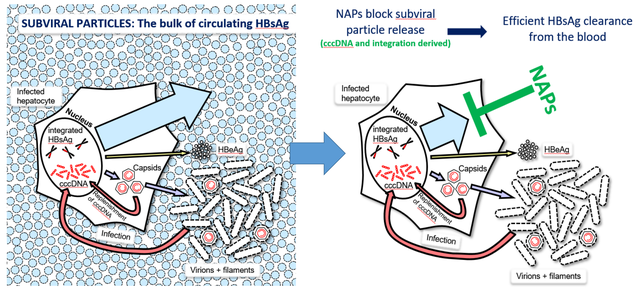
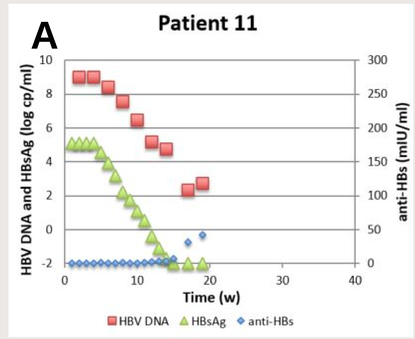
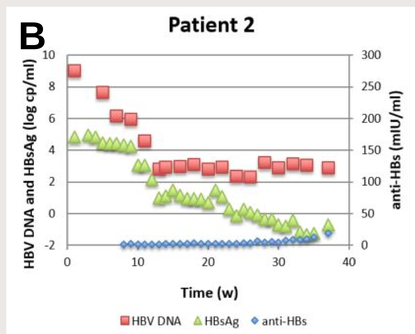


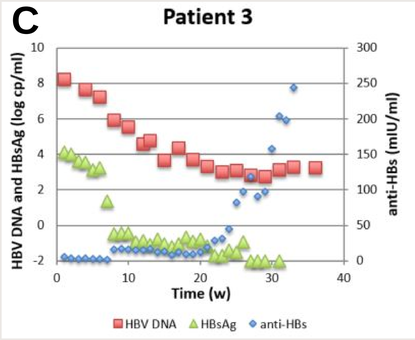
Figure 1. Mechanism of action of NAPs



Monophasic HBV DNA and HBsAg decline with anti-HBs appearance at week 17 post initiation of treatment.



Flat partial response HBV DNA kinetic pattern and straicase HBsAg decline manner with anti-HBs appearance at week 35 post initiation of treatment.



Biphasic HBV DNA decline pattern and triphasic HBsAg decline pattern with anti-HBs appearance at week 8 post initiation of treatment.

Figure 2. Representative HBV DNA, HBsAg and anti-HBs kinetic patterns during REP 2139 monotherapy (adapted from [1]).

CONCLUSIONS

- REP 2139 monotherapy led to a mono- or bi-phasic HBV VL decline and complex HBsAg inhibition patterns in 9 of 12 patients, with anti-HBs seroconversion in 6 of those 9.
- Kinetic analysis of the 1st HBsAg decline phase indicates a mean HBsAg $t_{1/2}$ of 5.3±3.2 d, which is strikingly shorter than estimated under approved medications, e.g., lamivudine [2] ($t_{1/2}$=38 d), and pegylated interferon-alpha [3] ($t_{1/2}$=32 d) suggesting REP2139 inhibits HBsAg release from infected hepatocytes.
- Further efforts are needed to refine the understanding of the modes of action of NAPs against HBV and HBV-host dynamics during treatment.

REFERENCES

1. **Al-Mahtab, Bazinet M, Vaillant A.** Safety and Efficacy of Nucleic Acid Polymers in Monotherapy and Combined with Immunotherapy in Treatment-Naive Bangladeshi Patients with HBeAg+ Chronic Hepatitis B Infection. 2016 PLOS One 11:e0156667
2. **Neumann AU, Phillips S, Levine I, Ijaz S, Dahari H, Eren R, Dagan S, Naoumov NV**. Novel mechanism of antibodies to hepatitis B virus in blocking viral particle release from cells. Hepatology (2010); Sep;52(3):875-85 .
3. **Moucari et al**. Early Serum HBsAg Drop: A Strong Predictor of Sustained Virological Response to Pegylated Interferon Alfa-2a in HBeAg-Negative Patients. HEPATOLOGY 2009;49:1151-1157.

ACKNOWLEDGEMENTS

The work was supported by Replicor Inc. and PETM.

DISCLOSURES

MB and AV are employees of and shareholders in Replicor Inc. The other authors have nothing to disclose.

CONTACT INFORMATION

Andrew Vaillant: availlant@replicor.com
Harel Dahari: hdahari@luc.edu