Modeling serum HBV DNA and HBsAg kinetics during nucleic acid polymer REP 2139 monotherapy in HBeAg+ chronically infected HBV patients

P-148

Louis Shekhtman[1,2], Nathaniel Borochov[1], Leeor Hershkovich[1], Scott J. Cotler[1], Susan L. Uprichard[1], Mamun Al-Mahtab[3], Michel Bazinet[4], Andrew Vaillant[4], Harel Dahari[4]

1. The Program for Exp. & Theor. Modeling, Division of Hepatology, Department of Medicine, Loyola University Medical Center, Maywood, IL, USA
2. Department of Physics, Bar-Ilan University, Ramat Gan, Israel
3. Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
4. Replicor Inc., Montreal, Quebec, Canada

BACKGROUND & AIMS

- Nucleic acid polymers (NAPs) are a new class of antiviral that significantly reduce circulating HBsAg and HBV DNA **(Fig.1)** and therefore provide a unique opportunity to study HBV-host dynamics. Here we estimate HBV kinetic parameters and REP 2139 efficacy against HBV during monotherapy in the REP 102 protocol (NCT02646189) using mathematical modeling.

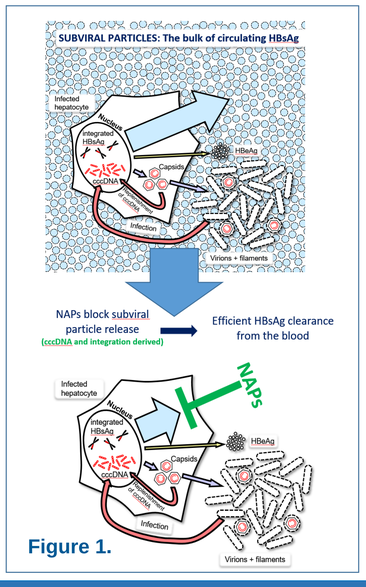

Figure 1.

METHODS

- Twelve HBeAg+ chronically infected HBV patients were given weekly 500mg IV infusions of REP 2139 for 20-40 weeks [1] **(Fig. 2)**. HBsAg and anti-HBs levels were measured weekly using quantitative Abbott Architect® assays. HBV DNA levels were measured biweekly using the Roche cobas® assay.

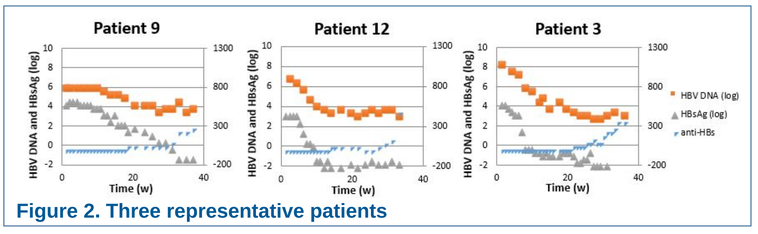

Figure 2. Three representative patients

- A mathematical model (Eq. 1) that incorporates HBV DNA and HBsAg kinetics was developed:

$$\frac{d}{dt}(I) = \beta T_0 V - \delta I$$

$$\frac{d}{dt}(V) = pI - m(t)cV \qquad (Eq.1)$$

$$\frac{d}{dt}(Sa) = (1-\varepsilon)p_s I - c_s Sa$$

where I represents HBV-infected cells, V HBV DNA, and Sa HBsAg (Sa). β is the infection rate constant, T_0 is the number of target cells, δ is the death rate of infected cells, p is the production rate of virions, c is clearance rate constant of virions, p_s is the production rate contant of HBsAg, and c_s is the clearance rate constant of HBsAg. Since all patients had pre-treatment anti-HBs<10 mIU/ml and anti-HBs only appeared in 6 patients (>10 mIU/ml, **Fig. 2**) during therapy and was not associated with viral load (VL) or HBsAg inhibition patterns, anti-HBs was not included in the model.

Drug efficacy in blocking HBsAg production is represented by parameter ε (0≤ε≤1). A time-dependent indirect drug effect m(t) that increases virus clearance is modeled as follows

$$m(t) = \min(m_{\max} 10^{(t-T)/\tau_1}, m_{\max})$$

where m_{max} represents the maximum increase in clearance, t is the time, τ controls when the increase in clearance begins, and τ_1 governs how quickly the increase to the maximum occurs. We note that the above equation for m is only valid when $t>\tau$, whereas for $t<\tau$ we set $m=1$.

RESULTS

Kinetic and Modeling Analyses

- Mean baseline VL and HBsAg were 7.9±1.3 Log cp/ml and 4.5±0.7 log IU/ml, respectively.
- Three non-responders with no decline in VL or HBsAg were excluded from modeling analysis.
- The model was able to reproduce well HBV DNA and HBsAg kinetics (**Fig. 3**) and model parameters were estimated (Table 1).
- Modeling predicts that HBsAg remained at baseline 50±45 days before a significant decline was observed.
- REP 2139 efficacy was >99% in blocking HBsAg production in 8 of 9 included patients.
- Average basal HBsAg clearance rate was 0.14±.07 day^{-1} corresponding of HBsAg $t_{½}$=5.0 days (range 2.9-11.2 days).
- Viral load remained at baseline 38±32 days before a significant decline was observed.
- Assuming that the indirect effects of REP 2139 (HBsAg clearance) is mainly viral clearance enhancement from blood (e.g., via restoration of immune response), modeling projects a 2694-fold increase in viral clearance per day (range 1-13409 fold per day) with mean maximum fold enhancement of 3.7±1.5 logs within 111±40 days post initiation of therapy.

Parameter	Value	Parameter	Value
β [1/virion/d]	10^{-7}	c_S [1/d]	0.058-0.29
T_0 [cells]	3.5×10^4-1.3×10^9	m_{max}	10^2-10^6
δ [1/d]	.00099-.051	T [d]	14-114
c [1/d]	0.50-0.74	T_1 [d]	19-121
ε	0.90-0.99999		

Table 1. Model parameter estimations. Parameters p and p_s were set by steady state initial (pre-treatment) conditions.

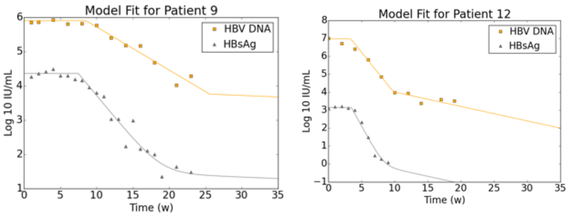

Figure 3. Representative model (Eq. 1) fits (solid lines) with data (circles). HBV DNA and HBsAg model curves were fitted simultaneously with measured data in each patient using Berkeley Madonna.

CONCLUSIONS & PERSPECTIVE

- REP 2139 monotherapy led to significant HBV VL and HBsAg inhibition in 9 of 12 patients.
- Modeling analysis of HBsAg indicates a mean HBsAg $t_{½}$ of 5.0 d (range 2.9-11.2 d), which is strikingly shorter than estimated under approved medications, e.g., lamivudine ($t_{½}$=38 d) and pegylated interferon-alpha ($t_{½}$=32 d).
- Modeling predicts that REP 2139 inhibits >99% of HBsAg release from infected hepatocytes in most patients.
- If REP 2139-mediated immune restoration is mainly via enhancement of viral clearance then modeling projects a mean 5000-fold increase in viral clearance.
- Further theoretical efforts and data 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, M., Bazinet, M., & Vaillant, A. (2016). Safety and efficacy of nucleic acid polymers in monotherapy and combined with immunotherapy in treatment-naive Bangladeshi patients with HBeAg+ chronic hepatitis B infection. PloS one, 11(6), e0156667.

CONTACT INFORMATION

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