Modeling serum HBV DNA, HBsAg and ALT kinetics during REP 2139 monotherapy in chronic HBeAg+ HBV patients

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INTRODUCTION

- Nucleic acid polymers (NAPs) block the secretion of HBV subviral particles (SVPs; **Fig.1**) without affecting secretion of Dane particles or intracellular levels of hepatitis B surface antigen, HBsAg [1].
- In hepatitis B e-antiegn (HBeAg+) chronic HBV infection, NAP monotherapy is associated with almost complete removal of circulating HBsAg and substantial reductions in serum HBV DNA [2].

AIM

To provide a mathematical model that predicts serum HBV DNA, HBsAg and alanine aminotransaminase (ALT) kinetic parameters during REP 2139 monotherapy in the REP 102 protocol (NCT02646189).

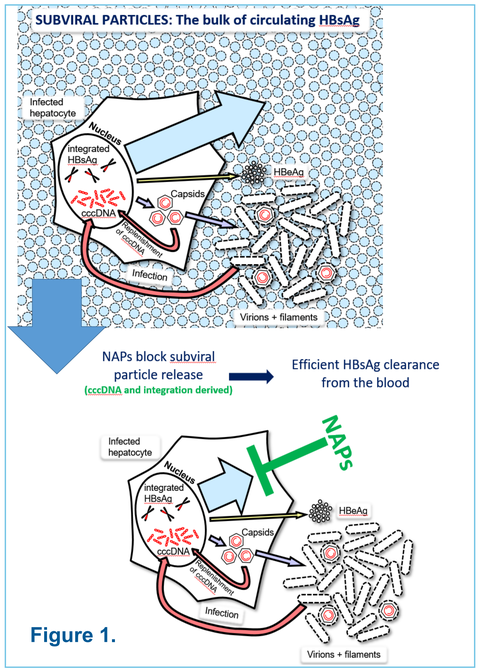
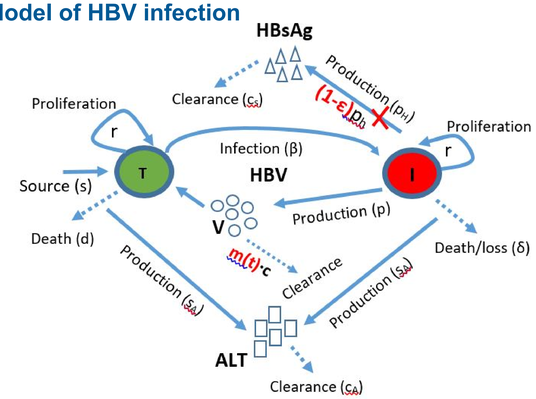


Figure 1.

METHOD

- Twelve HBeAg+ chronically infected HBV patients were given weekly 500mg IV infusions of REP2139 for 20-40 weeks [2].
- HBV DNA, anti-HBs, HBsAg and ALT levels were measured every 1-2 weeks during treatment **(Figs. 3 and 4).**
- A model (**Fig. 2**) that includes proliferation of uninfected and infected cells and accounts for HBV DNA, HBsAg and ALT dynamics was developed:

Figure 2. Model of HBV infection



where T, *I and V* represent target cells, HBV-infected cells, and *free* HBV DNA (virions), respectively. T+I can proliferate with maximum proliferation rate r, according to a blind homeostasis process. Treatment (parameters in red) may block HBsAg production with efficacy ε and enhance clearance rate of virions by a factor m(t) (Eq. 1).

- Since all patients had pre-treatment anti-HBs<10 mIU/ml and anti-HBs only appeared in 6 patients (>10 mIU/ml, **Fig. 3**) during therapy and was not associated with viral load (VL) or HBsAg inhibition patterns, anti-HBs was not included in the model.
- Three non-responders with no decline in HBV DNA and HBsAg were excluded.
- 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

$$m(t) = \min(m_{\max} 10^{(t-T)/\tau_1}, m_{\max}) \quad \textbf{Eq. 1}$$

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. Note: the above equation for m is valid when $t>\tau$, whereas for $t<\tau$ we set $m=1$.

RESULTS

- Mean baseline HBV DNA, ALT and HBsAg were 7.9±1.3 log copies/mL, 79±36 IU/L and 4.5±0.7 log IU/mL, respectively (**Figs. 3 and 4**).
- HBV DNA and HBsAg declined from baseline levels during therapy in 9 patients (**Figs. 3 and 4**).
- At the end of NAP monotherapy, mean ALT was lower than baseline (61±29 IU/L; p=0.2), however ALT flares (>3-fold increase) were observed in 4 patients between 4 and 9 weeks after therapy initiation (**Fig. 4**)
- Model fits indicate that HBsAg and HBV DNA declines started 36±32 days after introduction of REP 2139 and estimate a mean REP 2139 efficacy of 97% ± 4% in blocking HBsAg secretion.
- Assuming that REP 2139-mediated reductions in HBsAg allow for restoration of immune function, modeling projects a mean increase in the rate of viral clearance of 541-fold per day (range increase of 0.2-4544 fold per day) with mean maximum fold enhancement of 3.2 ± 1.2 logs within 110±35 days post therapy initiation.
- The model reproduces the observed ALT kinetics in the 5 patients without an ALT flare (**Fig. 4**).
- For patients who experienced an ALT flare, the model did not successfully replicate the ALT kinetics, but are consistent with assumed indirect immune clearance.

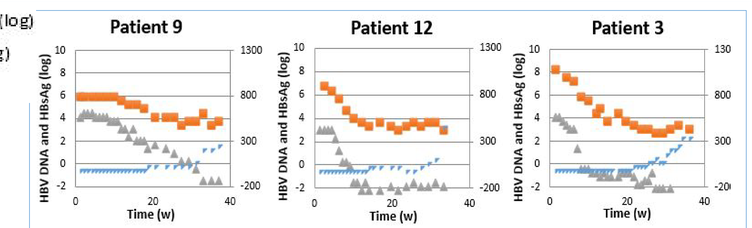


Figure 3. Three representative patients

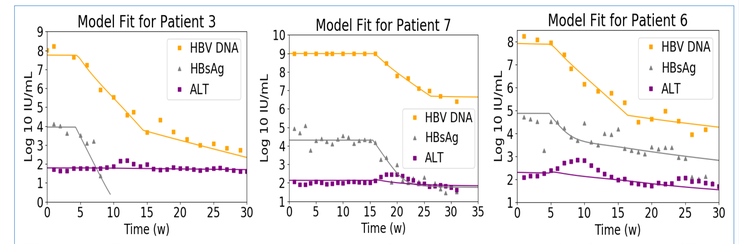


Figure 4. Representative patients' data (symbols) and model fit curves (Eq. 1)(solid lines). HBV DNA, ALT and HBsAg model curves were fit simultaneously with measured data in each patient using Berkeley Madonna. Patients 3 and 7 do not have an ALT flare and the model fits reasonably well. Patient 6 had an ALT flare and we thus see that the ALT does not fit will.

Parameter	Value	Parameter	Value
δ [1/d]	.0078-0.23	c_s [1/d]	0.14-0.28
c [1/d]	0.25-0.41	m_{max}	$10^{1.2}$-$10^{5.5}$
ε	0.90-0.9998	T [d]	11-109
c_{ALT} [1/d]	0.26-0.56	τ_1 [d]	55-90

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

CONCLUSIONS

- Modeling fits indicated a potent efficacy/enhancement in blocking HBsAg secretion and associated viral clearance.
- The delay observed before HBsAg and viral decline after introduction of REP 2139 was variable among patients and in some cases was decoupled, suggesting a variable state of immune function participating in the clearance of HBsAg versus HBV DNA.
- Further modeling efforts to refine the understanding of the modes of action of NAPs against HBV and the nature of ALT flares are ongoing.

REFERENCES

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2. Al-Mahtab, et al. (2016). PloS one, 11(6), e0156667

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