Characterization of optimal clinical trial design and best responders using mechanistic modeling - Application to Chronic HBV

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BACKGROUND

- Demonstrating safety and efficacy of developing drugs is long, high costing and presents important risks of failure.
- *In silico* trials predicting drug efficacy can be used to optimize clinical trial design and explore patient characteristics linked to treatment response.
- Application to Chronic Hepatitis B (CHB):
  - 350 million people affected worldwide [1].
  - Complex intertwined mechanisms: viral replication and host immune response.
  - No curative treatment among standards of care (nucleos(t)ide analogs, including entecavir [ETV] and immunostimulant peginterferon alfa-2a [IFN] mono or combined therapies).
    - Hepatitis B virus (HBV) serum markers remain or rebound after treatment.
    - High inter-patient variability in treatment response is observed.
  - Vonafexor (VFX), is a novel treatment candidate developed by ENYO [2] (Phase 2b trials to be designed).
- A mechanistic modeling approach enabled to
  - Simulate a high number of different treatment regimens for heterogeneous patients' profile.
  - Identify best regimens and best responders characteristics.

METHODS

- A knowledge-based mechanistic model was built and calibrated based on published literature and clinical trial data (Fig. 1).

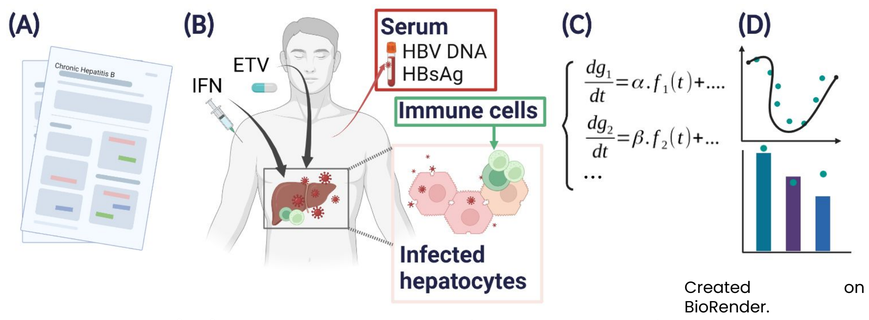

Figure 1. Model building process. Following an extensive literature review (A), a knowledge-based model is built (B) and translated into a mathematical model (C) calibrated to fit clinical data (D).

- 144 *in silico* trials were performed comparing VFX to placebo administered on top of IFN/ETV (VFX 0, 100, 200, 300 mg QD; IFN 180, 360 or 180 then 360 µg QW, 6 sequences and 4 durations) in a Virtual population where each patient is his own control (Fig. 2).

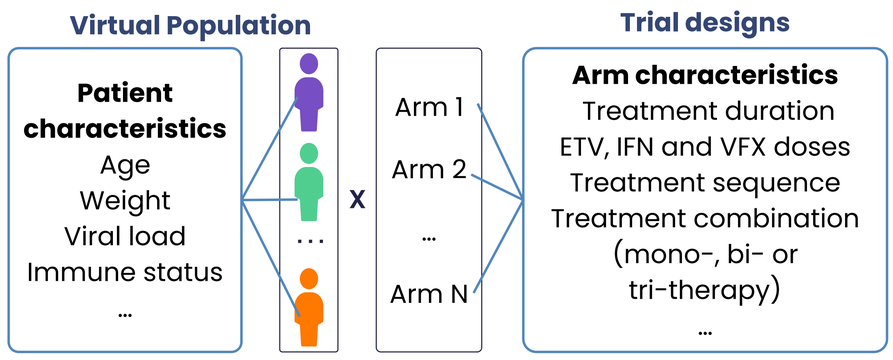

Figure 2. In silico protocol design.

MODEL DESIGN & CALIBRATION

- A multiscale mechanistic model of CHB pathophysiology combined with physiologically based pharmacokinetic (PBPK) and efficacy models of 3 treatments (ETV, IFN and VFX) (Fig. 3A) was built.
- Patient- and population-level dynamics of serum viral markers (SVMs) (Fig. 3B-C), immune and intra-hepatic viral markers in response to treatments were calibrated to reproduce *in vitro* and *in vivo* clinical data from (B) Zoulim et al. (2014) [3] and (C) Tangkivanich et al. (2015) [4].

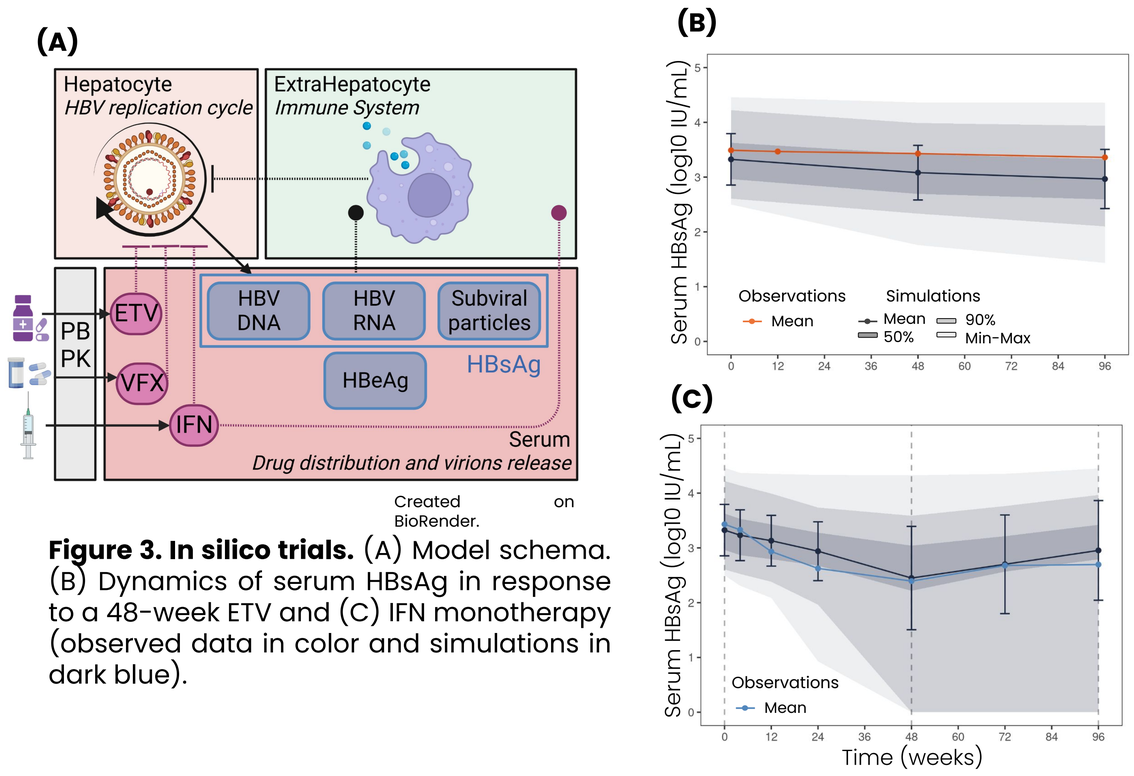

Figure 3. In silico trials. (A) Model schema. (B) Dynamics of serum HBsAg in response to a 48-week ETV and (C) IFN monotherapy (observed data in color and simulations in dark blue).

SIMULATIONS AND RESULTS

Predict patients response

- Baseline levels of intrahepatic and serum viral markers (including HBV DNA, RNA and HBsAg) and host immune markers (including IL-10, IFN-γ) were compared for simulated patients presenting high, medium or low response (in terms of HBsAg decrease) ETV and IFN monotherapies.
- Differences between high, medium and low treatment responders were more remarkable for immune and intra-hepatic viral markers than serum viral markers.
- Model results suggest a better prediction of patients' response through immune and intrahepatic viral markers than SVM baseline values.

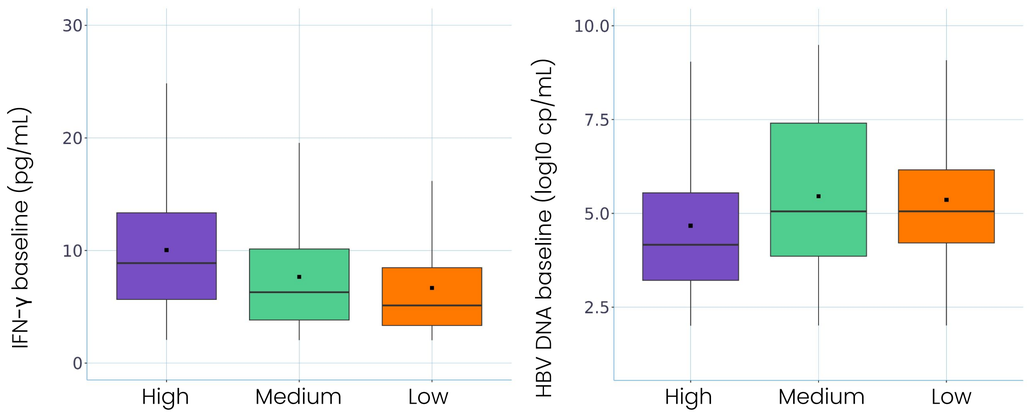

Figure 4. Best responders characteristics. Baseline (A) interferon-gamma (IFN-γ) and (B) serum HBV DNA for 3 categories of response to peg-IFN monotherapy (high, medium, low).

Explore best treatment designs

- Higher HBsAg decrease from baseline to end of treatment (EOT) were observed for VFX combined with IFN over 48-60 weeks (Fig. 5A-B).
- The model also predicted little additional benefit of the addition of ETV on top of IFN and VFX and from the highest IFN dose regimen compared to the hybrid dosing regimen.
- A random forest comparing all scenarios together identified VFX dose and treatment duration and IFN dose as the most impactful factors (Fig 5C).

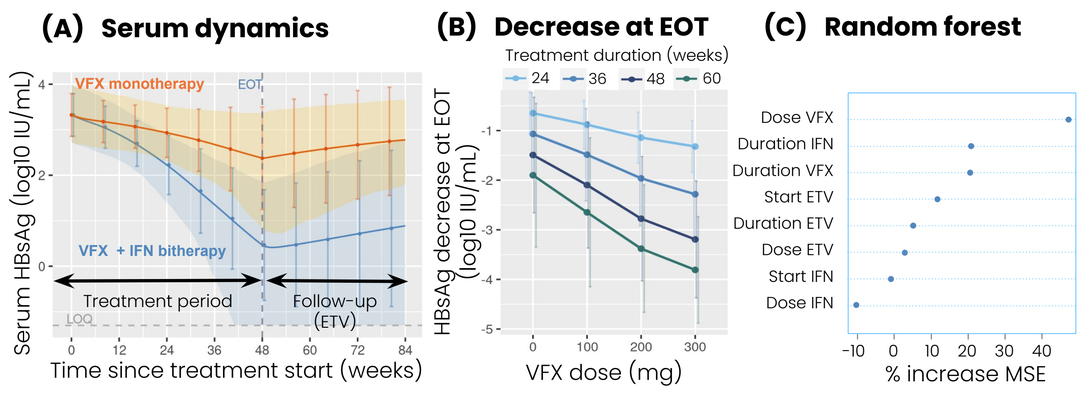

Figure 5. Impact of trial design features on serum HBsAg.

CONCLUSION

- A **mechanistic model accounting for drug and HBV disease related processes** was built.
- Based on published knowledge it enabled to **characterize contributions of complex biological mechanisms**, such as immune and viral intrahepatic characteristics, in response to treatments with few available quantitative data.
- In silico modelling offered the possibility to **test 144 trial designs on 1000 virtual patients to identify the best design** for the next Phase 2b clinical trial of Vonafexor, saving time and money and bringing new drugs to the appropriate patients faster.
- Similar mechanistic modeling approach can be used in other contexts:
  - Study interactions with co-infections, with hepatitis D virus for instance
  - Other disease types (cancers, dermatologic diseases…)
  - Explore new treatment targets and drugs interactions

ACKNOWLEDGMENTS

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