An in silico HBV model predicts viral response to the oral non-steroidal carboxylic acid FXR agonist EYP001a

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BACKGROUND

In line with the guidance of the FDA to expand the use of in silico trial simulations to support drug development [1], a mathematical model of hepatitis B virus (HBV) infection was built to simulate the effect of EYP001a treatment on HBV replication.

EYP001a is a synthetic non-bile acid Farnesoid X receptor (FXR) agonist currently under clinical development for chronic HBV infection and NASH. FXR regulates bile acid metabolism and is a target for liver disease therapies. We aimed at exploring the EYP001a effect on hepatocyte viruses and viral markers production.

METHODS

The mechanistic model was based on curated knowledge extracted from white and gray scientific literature via the community-driven knowledge management platform (https://github.com).

The complete model (140 ODEs, 359 parameters) integrated bile acids physiology, cholesterol metabolism, HBV replication and compound mode of action (the latter from EYP001a non-clinical data, Fig. 1).

The computational model was written and implemented through Novadiscovery’s proprietary simulation framework and its various tools (SimWork). The SimWork virtual population and exploration tools were used to calibrate the model: 1,000 virtual patients were randomly generated from ranges of descriptor (representing the n model parameters) values and were selected on the basis of a score translating physiological and biological constraints that the model should comply with; this results in an n-dimension space domain where the parameter values meet the constraints. Qualitative model validation was done through comparison of simulation outputs to known biological systems/disease dynamics.

An independent team, blinded to available clinical EYP001a data, simulated the effect of single and multiple oral doses of EYP001a in healthy or chronically infected HBV virtual subjects. EYP001a effects on FXR response markers 7α-Hydroxy-4-cholanoate-3 (C4) and FGF19 and their changes in vivo and in vitro HepaRG experiments and in vivo HBV infected subjects. The effect on HBV replication of several combinations of EYP001a dosing regimens was explored. Additionally, different associated daily dietary intakes of cholesterol schemes were tested. HBV DNA output curve was generated for 1,000 virtual HBV subjects treated for 100 days with EYP001a.

RESULTS

The model successfully reproduced EYP001a plasma concentration-time profiles (Cmax, Tmax and AUC) at the different tested doses (Fig. 2).

The model reproduced accurately the dynamics of C4 and FGF19 and their changes after single and multiple EYP001a administrations (Fig. 3a and Fig. 3b).

The differences in terms of efficacy between fasted and fed before the administered dose of 250mg were tested. HBV DNA output curve was generated for 1,000 virtual HBV subjects (Fig. 4).

The mean value and 95% CI of log10(copies of HBV DNA/mL) per treatment group is shown in Fig. 5. The two EYP001a treatment regimens (BID 200mg in green, QD 400mg in orange) are administered at t=0.

Various combinations of dosing regimens with associated cholesterol dietary intakes were tested (Fig. 5) and it was established that 200mg EYP001a BID dosing was an appropriate efficacious regimen (Fig. 6).

DISCUSSION & CONCLUSIONS

The in silico model reproduced well EYP001a plasma concentrations as well as the dynamics of C4 and FGF19 in blood.

The in silico model predicted the viral response in a virtual HBV infected population (1,000 virtual patients).

The strong predictability of our simulation approach using in silico modeling could be used to determine as a priori better dosing regimen in chronic HBV patients. We predicted a superior efficacy of the treatment when it is administered in two separate doses (BID 200mg) instead of only one full dose (QD 400mg). The average reduction of the number of viral particles tends to be higher among virtual patients who received two doses of 200mg.

The differences in terms of efficacy between fasted and fed before the administration of the treatment appear to be minimal. However, it is important to note that we did not integrate a complete and mechanistic model of nutrition (cholesterol dietary intake only).

Once quantitatively validated with data from both in vitro HepaRG experiments and in vivo HBV infected subjects, this in silico model will be used to explore other FXR agonist treatment strategies and to identify best responders in the population to be tested in coming phase II HBV trials.

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REFERENCES