An in silico disease model for the development of FXR agonist EYP001 as a therapy for HBV infection

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BACKGROUND

Chronic infection with hepatitis B virus (HBV) increases the risk of death from cirrhosis or liver cancer. The farnesoid X receptor (FXR) is an investigational target for HBV infection therapies in view of its putative role in modulating HBV replication and in decreasing the pool of intracellular HBV DNA. The FXR agonist EYP001 was well tolerated by healthy and HBV-infected subjects in a phase 1 study. In hepatocytes, EYP001 inhibited the *ex vivo* secretion of HBV DNA and the HBV antigens HBsAg and HBeAg, whereas the antiviral entecavir (ETV) reduced HBV DNA secretion only.

We suggest that therapies combining the FXR agonist EYP001 with standard treatments such as nucleoside analogs or interferons will increase chances of curing chronic hepatitis B through their highly probable synergistic effects in terms of immunomodulation and in decreasing HBV replication.

We used computational modeling to improve the design, dosage, timing, and patient selection for combination therapies based on EYP001 treatment.

METHODS

An *in silico* disease model of chronic HBV patients has been built based on public and expert knowledge, non-clinical, and clinical data.

The Computational Model is a system of differential equations that integrates 300+ biological variables and 600+ parameters. With 7 mechanistic submodels (including the effect of FXR agonist on HBV replication, HBV excretion, bile acid physiology and EYP001, ETV, and pegylated interferon [PEG-IFNα2a] drug models), the model has been used to predict quantitative efficacy of treatments on disease-related endpoints (eg. plasma HBV DNA and HBsAg concentrations) in a virtual population. All the submodels are ultimately combined into a multi-scale Computational Model simulating the dynamics of biological entities at the molecular, cellular and organ levels. Figure 1 illustrates the structure of the integrated Computational Model.

The Computational Model was written and implemented through Novadiscovery's proprietary simulation framework and its various tools (Jinkō). The virtual population and exploration tools were used to calibrate the model: 1,000 virtual patients were generated by randomly sampling from a set distribution for each of descriptors (representing the n model parameters). Virtual patients were ranked and selected on the basis of a score translating physiological and biological constraints that the model should comply with, as well as data from Phase I studies. This results in a n-dimension space domain where the parameter values meet the constraints.

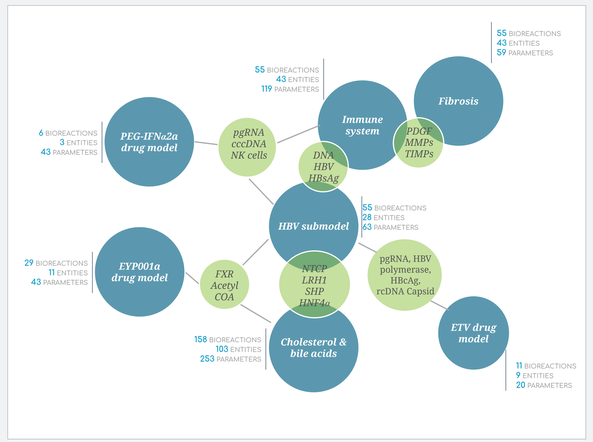

Figure 1: Computational Model structure: submodels are shown as blue circles and entities used as connectors for the submodels are shown as green circles.

These simulated results will be quantitatively validated with data from upcoming Phase II studies.

The model has been used to explore the effects of multiple combinations of EYP001 with ETV and/or PEG-IFNα2a therapies via the simulation of an *in silico* Phase II trial. We compared different combinations of treatments according to the following factors:

- Drug combination (no treatment, EYP001a monotherapy, EYP001a + ETV & EYP001a + PEG-IFNα2a bitherapies, EYP001a + ETV + PEG-IFNα2a tritherapy).
- Treatment duration (24 & 48 weeks).

We also simulated the effect of run-in periods (ETV 1 month, PEG-IFNα2a 1 month, ETV 4 months, PEG-IFNα2a 4 months, tritherapy 1 month) before the administration of treatment combinations.

RESULTS

Phase 1 results were well reproduced *in silico*, including the effects of EYP001 on the FXR response markers 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF19) (Figures 2 and 3), and on HBV DNA plasma concentrations.

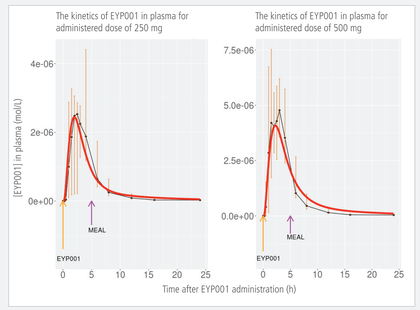

Figure 2: Kinetics of EYP001a in plasma for the administered doses of 250 mg (left panel) and 500 mg (right panel). The black dots and the brown bars represent the median and the minimum-maximum range of experimental data, respectively. Red solid lines correspond to the EYP001a simulated concentrations.

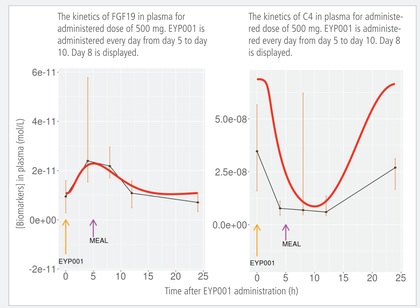

Figure 3: Kinetics of FGF19 (left panel) and C4 (right panel) biomarkers in plasma for the administered dose of EYP001a of 500 mg. Black dots separated by black lines and brown bars represent the median data and the minimum-maximum range of experimental data, respectively. Red solid lines represent the simulated concentration of biomarkers.

The model accurately predicts the short-term impact of FXR agonism on FGF19 concentrations and its impact in reducing HBV DNA and HBsAg concentrations (Figures 4 and 5).

In silico Phase II trial simulations allowed us to identify the 24-week bi-therapy of EYP001 and PEG-IFNα2a as the best combination in reducing plasma HBV DNA and HBsAg levels, and in minimizing relapse after a 24-week follow-up period (Figures 4 and 5). The percentage of relapsing patients 2 months after the end of 24-week treatment was 26.5% for the bitherapy with EYP001 QD 400 mg + PEG-IFNα2a, whereas it was of 94.2% for patients receiving PEG-IFNα2a only, and 100% for the no treatment group.

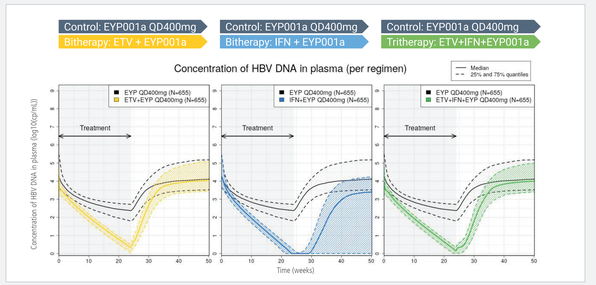

Figure 4: HBV DNA levels in plasma (log10 (copies/mL)) after 24 weeks of treatment and 24 weeks of follow-up. Comparison of control (EYP001a QD 400 mg) with ETV + EYP and IFN + EYP bitherapies and EYP + IFN + ETV tritherapy. (ETV: entecavir; IFN: pegylated interferon alfa-2a; EYP: EYP001a).

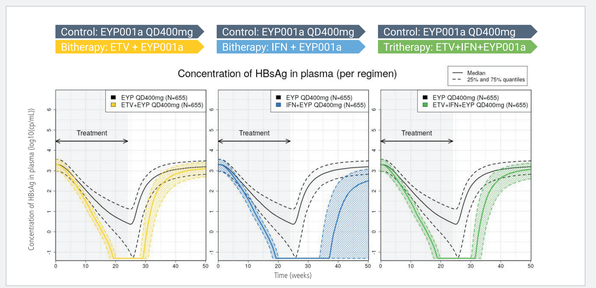

Figure 5: HBsAg levels in plasma (log10 (copies/mL)) after 24 weeks of treatment and 24 weeks of follow-up. Comparison of control (EYP001a QD 400 mg) with ETV + EYP and IFN + EYP bitherapies and EYP + IFN + ETV tritherapy. (ETV: entecavir; IFN: pegylated interferon alfa-2a; EYP: EYP001a).

DISCUSSION & CONCLUSIONS

- To date, and despite decades of research, there is still no curative treatment for chronic hepatitis B. The last few years have seen an increased interest for combination of antiviral therapies with the common objective of increasing the rate of HBV eradication.
- We used computational modeling to improve the design, dosage, timing, and patient selection for combination therapies based on EYP001 treatment.
- The *in silico* model reproduced well all drugs plasma concentration profiles as well as their independent characteristics and effects.
- These preliminary results suggest EYP001 combined with PEG-IFNα2a is an optimal regimen and support selection of EYP001 regimens in Phase 2 trials.
- Next step will include best virtual responders characterization for patients selection of the next clinical trial.

ACKNOWLEDGEMENTS

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