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 I 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 nucleotide 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 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 60+ 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 dynamic behaviors of 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 (Jinite). 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.

RESULTS

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

We simulated the effect of run-in periods (ETV 1 month, PEG-IFNα2a 1 month, ETV 4 months, PEG-IFNα2a 4 months, 3 months treatment 1 month) before the administration of treatment combinations.

The model accurately predicts the short-term impact of FXR agonism on FGF19 concentrations and its impact in reducing HBV DNA and HbsAg levels. These preliminary results suggest EYP001 combined with PEG-IFNα2a as an optimal regimen and support selection of EYP001 regimens in Phase 2 trials.

The next step will include best virtual responders characterization for patients selection of the next clinical trial.

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REFERENCES

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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 individual characteristics and effects.

These preliminary results suggest EYP001 combined with PEG-IFNα2a as an optimal regimen and support selection of EYP001 regimens in Phase 2 trials.

The next step will include best virtual responders characterization for patients selection of the next clinical trial.