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Predicting the Efficacy of Obeticholic Acid Treatment for Non-Alcoholic Steatohepatitis (NASH) Using NAFLDsym, a Quantitative Systems Pharmacology Model of Non-Alcoholic Fatty Liver Disease

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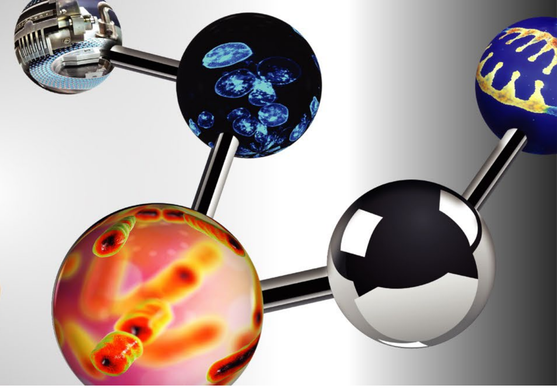


PURPOSE

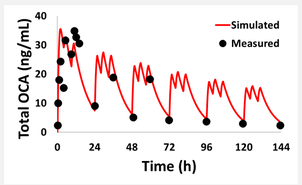
Obeticholic acid (OCA), a bile acid analog and agonist of the farnesoid X receptor (FXR), is currently in clinical trials for the treatment of non-alcoholic steatohepatitis (NASH). Decreases in plasma transaminases and liver fat content have been reported after 72 weeks of OCA treatment in Phase 3 studies (1,2). Other FXR agonists have indicated that they are targeting intestinal FXR (and subsequent hepatic effects of increased FGF19), whereas OCA may have the ability to target both intestinal and hepatic FXR.

The purpose of this work was to represent OCA using quantitative systems pharmacology (QSP) modeling and to understand whether OCA's effects are primarily due to liver or gut FXR.

METHOD(S)

PBPK Modeling

A PBPK model of OCA was constructed in MATLAB based on the parameters presented in Edwards 2014 (3, below). It was then adjusted in order to fit data from multiple-dose OCA treatment reported in the FDA documentation for OCA.



QSP Modeling

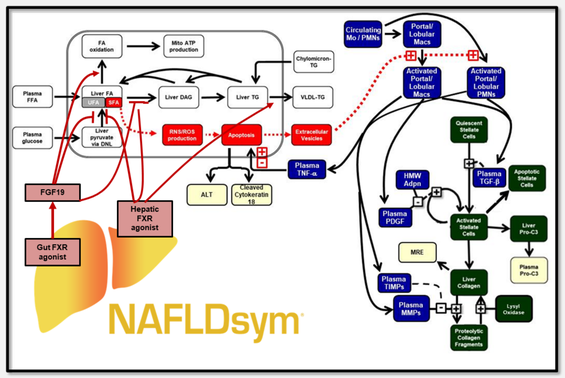
A QSP representation of OCA was constructed in NAFLDsym v2A. FGF19 production via gut FXR activation and bile acid synthesis inhibition (via plasma C4 concentration) were parameterized based on literature data (4-6). Liver FXR effects were then parameterized based on the clinical data (2,7). Population-based simulations were then run in simulated patients with liver fibrosis at stages 3 and 4.

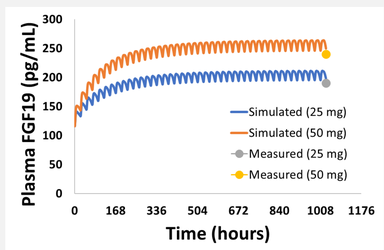
RESULTS

QSP Modeling

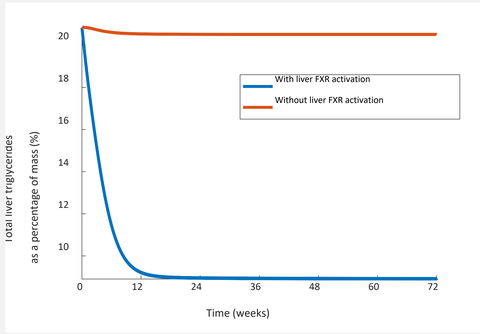
- Activation of liver FXR and the effects of liver FXR were represented within NAFLDsym v2A (below).
- NAFLDsym recapitulated the increase in plasma FGF19 generated by OCA in clinical trials (6).
- The model correctly recapitulated the clinical decrease in liver fat and predicted the percentage of individuals with a decrease in fibrosis by >1 stage as reported in clinical trials.
- The modeling demonstrates that the activation of liver FXR is necessary to recapitulate the clinical effects of OCA.

Below: Diagrammatic representation of NAFLDsym showing how liver FXR activation by OCA was represented.

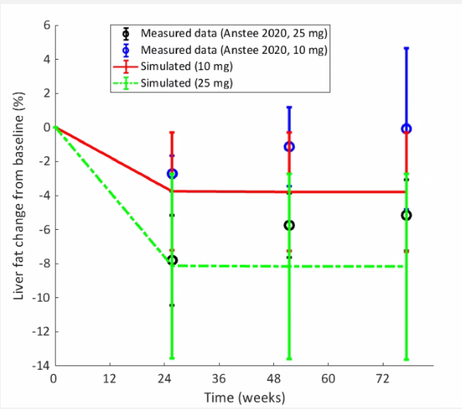




Right: Simulated plasma FGF-19 due to OCA administration and comparison to clinical data (6).



Above: Simulated effect of OCA on liver fat in a single simulated individual with and without liver FXR activation included in the representation. This demonstrates the importance of liver FXR activation in the mechanism of action of OCA.



Above: Simulated liver fat change from baseline due to OCA administration and comparison to clinical data (1). Below: Simulated change in fibrosis score and NAFLD Activity Score (NAS) in a simulated population compared to clinical data (1,7).

Measure	OCA Dose (mg)	Clinical Data	Simulation Results
Fibrosis Reduction >1 stage	10	17.6% of individuals	22% of individuals
	25	23.1% of individuals	25% of individuals
NAS reduction	25	1.4 (average)	1.3 (average)

CONCLUSION(S)

The modeling suggests that the effects of OCA are mainly due to the activation of liver FXR, and that liver FXR activation reduces liver fat by decreasing hepatic conversion of fatty acids to triglycerides, decreasing hepatic de novo lipogenesis and increasing fatty acid oxidation.

NAFLDsym modeling provided insight into the potential hepatic lipid trafficking mechanisms of action of OCA, demonstrating the importance of liver FXR activation to its therapeutic effect. This model will be useful for predicting the effects of other FXR agonists and comparing them to OCA.

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