Using Quantitative Systems Pharmacology Modeling to Understand the Effects of Acetyl CoA Carboxylase (ACC) Inhibition on Liver and Plasma Triglycerides in a Simulated Population

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ABSTRACT

Treatment options for nonalcoholic steatohepatitis (NASH) are limited. One approach targets hepatic acetyl-CoA carboxylase (ACC), which influences de novo lipogenesis (DNL) and fatty acid oxidation. An oral, liver-targeted ACC inhibitor, GS-0976, has demonstrated reductions in hepatic fat, liver biochemistry, and markers of fibrosis in pre-clinical and clinical studies. However, increased plasma triglycerides (TG) have been observed in some patients, warranting mechanistic investigation. Quantitative systems pharmacology (QSP) approaches can help evaluate hypotheses by simulating alternative mechanistic pharmacodynamic (PD) effects. The QSP mathematical model, NAFLDsym, simulates inter-patient pathophysiologic variability in pathways that contribute to steatosis and lipotoxicity in NAFLD and NASH patient populations (SimPops). Mechanistically, NAFLDsym v1A includes hepatic steatosis, lipotoxicity, plasma TG, liver injury and regeneration, and biomarkers (e.g., ALT).

NAFLDsym v1A was used to predict reductions in liver TG and plasma ALT in addition to plasma TG increases following treatment with the ACC inhibitor GS-0976. Following simulations of previous clinical studies (Stiede 2017 [1], Lawitz 2018 [2]), additional predictions of GS-0976 treatment (5 or 20 mg q.d.) for 12 weeks (ClinicalTrials.gov NCT02856555 [3]) were performed in the SimPops; the simulations included the following PD mechanisms in various combinations: A) DNL inhibition, B) increased VLDL-TG secretion, C) lipoprotein lipase (LPL) inhibition.

Significant reductions in liver fat and plasma ALT were predicted for both GS-0976 doses when PD mechanisms A, B, and C were all employed. Plasma TG were predicted to increase in several simulated patients. These simulation results were comparable with observed clinical patient data from a phase 2 trial (NCT02856555) of GS-0976 [3]. However, simulation results absent any one or two of the PD mechanisms did not agree with the clinical data, suggesting the clinical response to ACC inhibition requires DNL inhibition, increased VLDL-TG secretion, and LPL inhibition. Simulated patients with exaggerated predicted plasma TG increases included notable LPL inhibition.

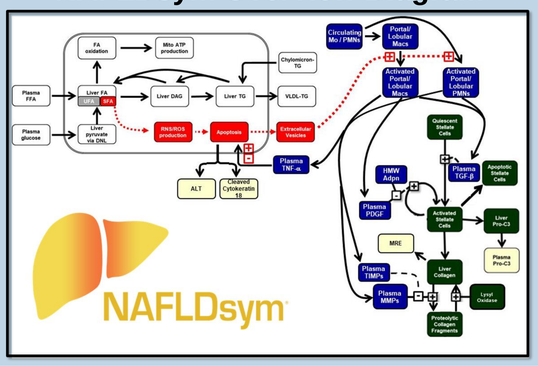
The NAFLDsym predictions suggest that liver fat and plasma ALT reductions in patients treated with GS-0976 are due to DNL inhibition and increased VLDL-TG secretion, while plasma TG increases are due to increased VLDL-TG secretion and LPL inhibition.

INTRODUCTION

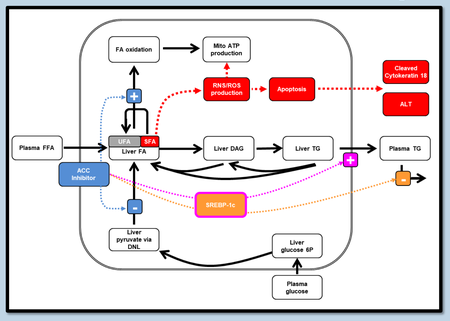
- GS-0976 is an ACC inhibitor that has been reported to inhibit DNL [1] and effectively reduce liver fat and plasma ALT in NAFLD and NASH patients [2,3]
- Some patients had Grade 3 or 4 hypertriglyceridemic responses to GS-0976 treatment; treatment with fibrates or fish oil effectively lowered plasma TG in these patients [3]
- NAFLDsym a QSP model of NAFLD pathophysiology, was used to predict reductions in liver fat and plasma ALT in addition to plasma TG increases to gain a better understanding of the mechanisms contributing to these responses

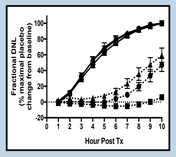
RESULTS

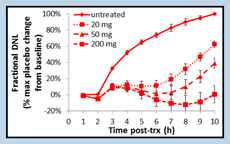
NAFLDsym Overview Diagram



Representation and Optimization of ACC Inhibition in NAFLDsym







Description

- GS-0976 potently inhibits both ACC1 and ACC2, leading to reduced de novo lipogenesis and increased fatty acid oxidation [1]. These PD effects were included in the simulations
- The simulations also included additional downstream effects to increase VLDL-TG secretion rates and to decrease plasma TG clearance
- The GS-0976 inhibitory effects on de novo lipogenesis were recapitulated with NAFLDsym simulations of the oral fructose challenge protocol (bottom) [1,9]

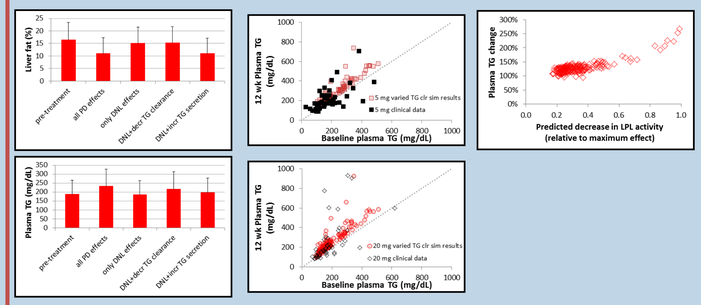
Accurate Prediction of Phase II Clinical Response to GS-0976 with NAFLDsym

Measure	Dose	Sampling time	Clinical data	Simulation results
Liver fat (%)	20 mg	Baseline	16.3	16.5
Liver fat (%)	20 mg	Week 12	11.6	11.0
Liver fat (%)	5 mg	Baseline	16.4	16.5
Liver fat (%)	5 mg	Week 12	14.9	12.7
Plasma TG (mg/dL)	20 mg	Baseline	181.3	187.3
Plasma TG (mg/dL)	20 mg	Week 12	251.9	231.9
Plasma TG (mg/dL)	5 mg	Baseline	173.3	187.3
Plasma TG (mg/dL)	5 mg	Week 12	209.8	223.1
Plasma ALT (U/L)	20 mg	Baseline	64.7	69.9
Plasma ALT (U/L)	20 mg	Week 12	49.8	48.4
Plasma ALT (U/L)	5 mg	Baseline	70.2	69.9
Plasma ALT (U/L)	5 mg	Week 12	65.9	56.9

Description

- NAFLDsym accurately predicted (red) clinical responses (black) at 5 mg and 20 mg doses in representative NASH SimCohorts
- GS-0976 effectively reduced liver fat in NASH patients after 12 weeks of treatment [3]
- Plasma ALT was also reduced with GS-0976 treatment [3]
- 14% of patients receiving GS-0976 had clinically asymptomatic hypertriglyceridemia [3]

Mechanistic Simulation Analyses of GS-0976 Effects on Lipids

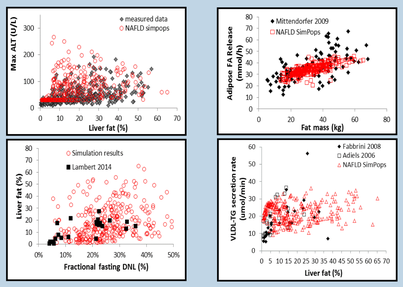


Description

- Only NAFLDsym simulations employing all mechanisms predicted comparable changes to liver fat and plasma TG (*left*)
- A small number of clinical and simulated patients had hypertriglyceridemic responses to GS-0976 treatment (*middle*)
- The simulated patients with the greatest increases in plasma TG had the greatest effect on LPL inhibition (*right*)

NAFLD SimPops Validation

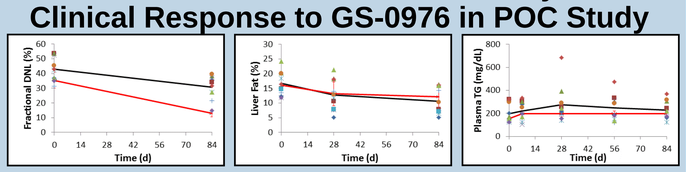
Variables Used to Construct the NAFLD SimPops™
Body weight
Adipose FA release
De novo lipogenesis
RNS-ROS clearance
Mitochondria function
VLDL-TG secretion rates
Plasma glucose
Hepatic glucose uptake
Plasma TG clearance
Apoptotic sensitivity to RNS-ROS
Necrotic sensitivity to ATP reductions
Hepatocyte regeneration



Construction and validation of NAFLD SimPops

- Simulated NAFLD patients (n=304) include combinations of parameter ranges based on reported responses from literature [4-8].
- Simulated patients within SimPops have pathophysiologic and clinical characteristics consistent with what has been reported in literature [4-8]

Accurate Simulation with NAFLDsym of Clinical Response to GS-0976 in POC Study



Description

- NAFLDsym accurately predicted the clinical response to 12 weeks of treatment with 20 mg GS-0976 while including direct effects of ACC inhibition on de novo lipogenesis in addition to downstream, indirect effects on VLDL-TG secretion rates and plasma TG clearance
- GS-0976 treatment led to reductions in DNL and liver fat [2]
- Plasma TG increased in some patients with GS-0976 [2]
- Simulations absent either downstream, indirect effects (indirect effects on VLDL-TG secretion rates and plasma TG clearance) did not agree with the clinical data (*not shown*)

METHODS

Overview NAFLDsym is a mechanistic, mathematical, QSP model that was utilized for all simulations. NAFLDsym includes a representation of the primary pathways controlling liver fatty acid and triglyceride fluxes in addition to the effects of lipotoxicity on hepatocellular health. NAFLDsym v2A also contains submodels describing the pathophysiology of inflammation and fibrosis; these submodels were not used for the simulations described herein. The primary simulated NAFLDsym outputs utilized were ALT, liver fat, and plasma TG.

Simulated patients A simulated population of patients with the pathophysiological aspects of NAFLD are included in NAFLDsym. This SimPops (n=306) includes a number of characteristics that are consistent with the observed heterogeneity of pathophysiologic and clinical features of NAFLD. For this study, a subset of all simulated patients (SimCohorts, n=144) with similar characteristics as the clinical cohort was utilized.

Simulated effects of ACCi ACC inhibition has been demonstrated to inhibit DNL and enhance fatty acid oxidation. These direct effects of ACC inhibition were represented within NAFLDsym and were optimized to available PD data [1]. Additional hypotheses regarding downstream, indirect effects of ACC inhibition were also evaluated. Increased VLDL-TG secretion rates and decreased plasma TG clearance pathways were also included in NAFLDsym simulations. Comparisons of simulation results with combinations of these effects with clinical data from the POC study [2] were used to confirm the magnitude of each effect was properly implemented within NALFDsym. In mechanistic analyses simulations designed to reveal which mechanisms were primarily responsible for the observed clinical responses, specific PD effects were inactivated.

Hepatocyte GS-0976 concentrations were predicted using PBPK modeling approaches. Predicted plasma GS-0976 profiles aligned well with clinical PK data (*not shown*)

Simulated Protocols A recently-completed 12 week phase II study trial was simulated [3]. 12 weeks of 5 mg or 20 mg q.d. GS-0976 treatment was simulated. Previous clinical protocols from a POC study (12 weeks, 20 mg q.d. GS-0976) and a clinical target engagement study (acute dosing of 20 mg, 50 mg, or 200 mg GS-0976 while periodically consuming oral fructose over 10 hours) were also simulated.

CONCLUSIONS

- NAFLDsym predictions of 12 weeks of treatment with the ACC inhibitor, GS-0976, indicate that:
  - Liver fat and plasma ALT reductions are due to a combination of DNL inhibition and increased VLDL-TG secretion
  - Plasma TG increases are primarily due to LPL inhibition with some contributions from increased VLDL-TG secretion as well

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