Mathematical Modeling with NAFLDsym Supports the Role of Adiponectin in the Reduction of Steatosis by the Anti-FGFR1/KLB Bispecific Antibody

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ABSTRACT

The agonist anti-FGFR1/KLB bispecific antibody, BFKB8488A, has been shown to be effective at reducing liver fat in NAFLD patients in a Ph1b study [1]. However, FGFR1/KLB receptors are primarily expressed in adipose rather than liver, suggesting a role for adipokine mediators such as adiponectin (Adpn). Adpn levels have been shown to increase with BFKB8488A treatment. NAFLDsym, a QSP mechanistic, mathematical model of NAFLD and NASH, was employed to evaluate the plausibility of Adpn increases mediating the reduction in liver fat observed with BFKB8488A treatment.

Exposure of BFKB8488A was predicted from PopPK modeling and combined with a mechanistic representation of the effects of BFKB8488A interaction with the FGFR1/KLB complex in adipose. The mechanistic model incorporated the effects of increased Adpn to elicit changes in several hepatic pathways that can act in concert to reduce the hepatic lipid burden. This included decreases in hepatic de novo lipogenesis and mono-acyl glycerol transferase activity along with an increase in hepatic fatty acid oxidation. Subcutaneous administration of 50 mg Q2W, 75 mg Q2W, 100 Q2W or 250 Q4W BFKB8488A was simulated for 12 weeks in a virtual cohort of NAFLD patients with steatosis (n=42).

Generally, simulations of BFKB8488A-mediated increases in Adpn were able to predict comparable reduction in liver fat as those observed in the Ph1b study. Simulated BFKB8488A administration was predicted to increase serum Adpn 40-80% over 12 weeks of dosing in an exposure-related manner (Figure 1), which was within range of the clinical data (except for 100 mg Q2W). Liver fat reductions were predicted to increase in magnitude with increasing dose within the simulated patient population, ranging from 0% to >90% relative to baseline. The inter-patient variability in the liver fat reduction was reasonably predicted. Alternative simulations without Adpn increase did not predict any effects on liver fat

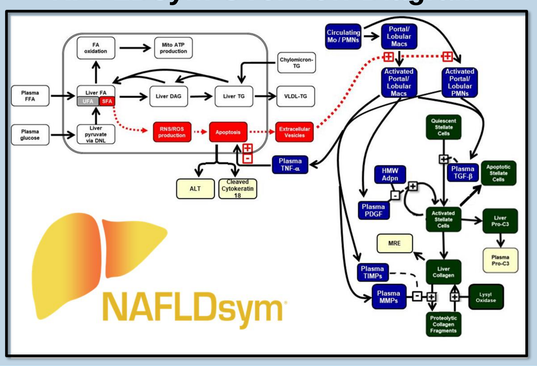
The hypothesis that BFKB8488A-induced increases in Adpn mediate the observed effects on liver fat in NAFLD patients is consistent with NAFLDsym simulations. The similarity between the clinical observations and model predictions utilizing the simulated mechanistic effects of Adpn on hepatic lipid pathways suggests that Adpn participates in mediating the potentially beneficial response to BFKB8488A.

INTRODUCTION

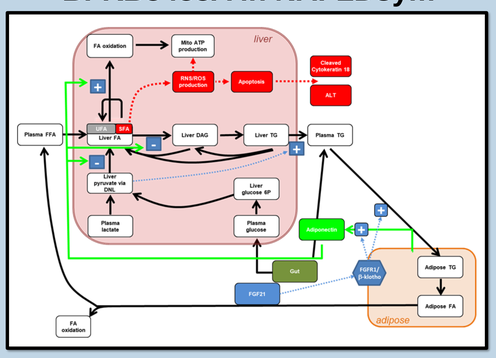
- BFKB8488A, an agonist anti-FGFR1/KLB bispecific antibody, has been shown to be effective at reducing liver fat in NAFLD patients in a Ph1b study (Kunder et al., AASLD 2019)
- FGFR1/KLB receptors are primarily expressed in adipose rather than liver, suggesting a role for adipokine mediators such as adiponectin (Adpn). Adpn levels have been shown to increase with BFKB8488A treatment
- NAFLDsym, a QSP model of NAFLD pathophysiology, was employed to evaluate the plausibility of Adpn increases mediating the reduction in liver fat observed with BFKB8488A treatment

RESULTS

NAFLDsym Overview Diagram



Representation and Optimization of BFKB8488A in NAFLDsym

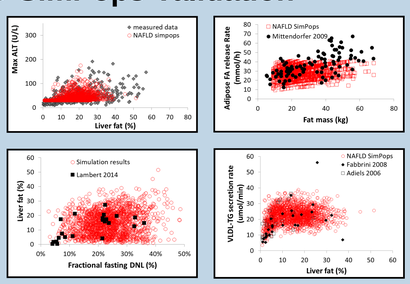


Description

- BFKB8488A agonist anti-FGFR1/KLB acts on adipose tissue to increase adiponectin secretion from the adipose and increase uptake of triglycerides from the plasma to the adipose. These PD effects were included in the simulations
- The simulations also downstream effects in the liver mediated by changes in the adiponectin receptor which stimulates AMPK [2-4]; these changes decrease de novo lipogenesis, decrease processing of saturated fatty acids into mono-, dia-, and triglycerides, increase liver secretion of triglycerides, and increase fatty acid oxidation [5-7].

NAFLD SimPops Validation

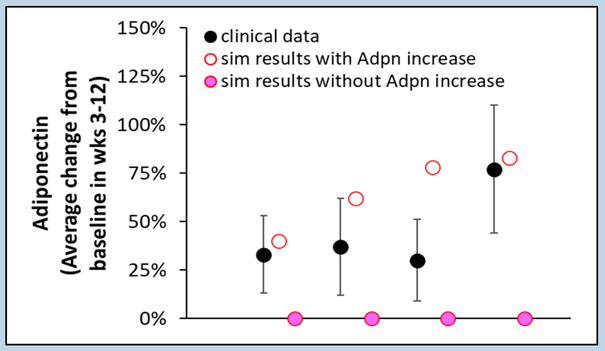
Variables Used to Construct the NAFLD SimPops™
Body weight
Adipose FA release
De novo lipogenesis
RNS-ROS clearance
Mitochondria function
VLDL-TG secretion rates
Plasma glucose
Hepatic glucose uptake
Plasma TG clearance
Apoptotic sensitivity to RNS-ROS
Necrotic sensitivity to ATP reductions
Hepatocyte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



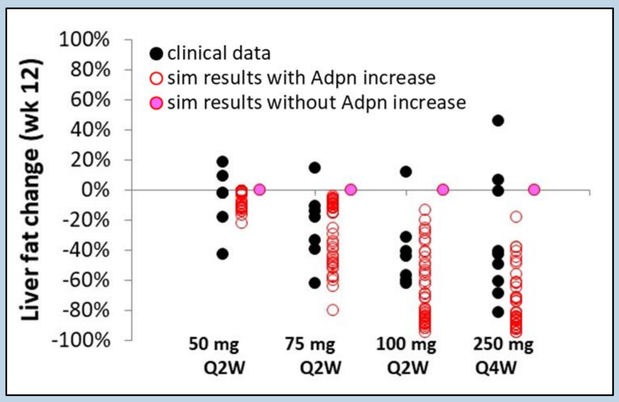
Construction and validation of NAFLD SimPops

- Simulated NAFLD patients (n=1707) include combinations of parameter ranges based on reported responses from literature [8-12].
- Simulated patients within SimPops have pathophysiologic and clinical characteristics consistent with what has been reported in literature [8-12]

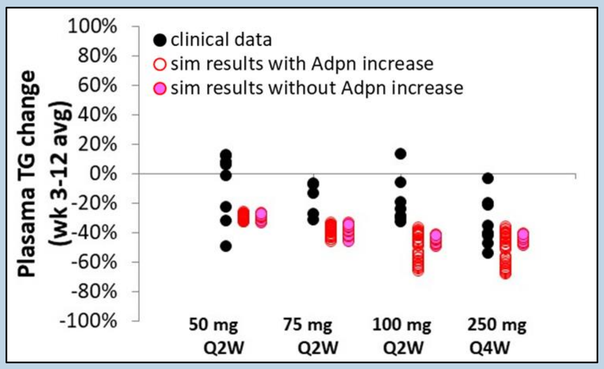
Accurate Prediction of Phase I Clinical Response to BFKB8488A with NAFLDsym



- NAFLDsym accurately predicted (red) clinical responses (black) for adiponectin (Adpn) in representative SimCohorts
- NAFLDsym simulations parameterized without Adpn increase (pink) did not represent clinical Adpn response



- NAFLDsym accurately predicted (red) clinical responses (black) for liver fat in representative SimCohorts, based on dose-dependent Adpn increases mediating liver effects
- NAFLDsym simulations parameterized without Adpn increase (pink) did not represent clinical liver fat response



- NAFLDsym reasonably predicted (red) the clinical responses (black) for plasma TG changes in representative SimCohorts, accounting for wide clinical variability in plasma TG responses

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 the focus for the simulations described herein. The primary simulated NAFLDsym outputs utilized were adiponectin, 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=1707) 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=42) with similar characteristics as the clinical cohort was utilized.

Simulated effects of BFKB8488A High molecular weight (HMW) adiponectin has been shown to increase the activity of hepatocellular AMPK following its interaction with the ADIPO R1 and R2 receptors [2-4]. In separate studies employing pharmacologic activators of AMPK in hepatocytes or HepG2 cells, AMPK activity has been demonstrated to reduce the expression and/or activity of ACC and FAS [5]. These are rate controlling enzymes of the de novo lipogenesis (DNL) pathway; reductions in expression/activity of these enzymes reduce flux through the DNL pathway. ACC also regulates the entry of fatty acids into the mitochondria; reduced ACC activity allows for greater fatty acid entry into the mitochondria to support fatty acid oxidation [6]. Additional studies have shown that AMPK activation reduces the hepatocellular expression/activity of MGAT, one of the enzymes that participates in the esterification of fatty acids to triglycerides [7]. Exposure-response relationships between HMW adiponectin and DNL inhibition, enhanced fatty acid oxidation, enhanced VLDL-TG secretion, and inhibition of fatty acid esterification, respectively were included within NAFLDsym v2A.

A subset of Genentech's ANTI-FGFR1/KLB MAB Phase Ib clinical data (50 mg Q2W and 250 mg Q4W) were used to optimize the quantitative relationships of each effect; the quantitative relationships based on the in vitro studies [5], [7] were not employed due to uncertainty of translating the quantitative aspects to humans. Validation of the optimized quantitative effects on DNL inhibition, fatty acid oxidation, and MGAT inhibition was performed by comparing simulation results with additional Phase Ib clinical data (75 mg Q2W and 100 mg Q2W).

Simulations were also conducted without parameterizing an adiponectin increase, to test the key method of action hypothesis for BFKB8488A.

Simulated Protocols Subcutaneous administration of 50 mg Q2W, 75 mg Q2W, 100 Q2W or 250 Q4W BFKB8488A was simulated for 12 weeks in a virtual cohort of NAFLD patients with steatosis

CONCLUSIONS

NAFLDsym simulated predictions of 12 weeks of treatment with the agonist anti-FGFR1/KLB bispecific antibody BFKB8488A indicate that:

- BFKB8488A administration was predicted to increase serum Adpn 40-80% over 12 weeks of dosing in an exposure-related manner, within the clinical data range
- Liver fat reductions in the simulated patients were predicted to increase in magnitude with increasing dose, and simulated magnitudes were consistent with the observed liver fat reduction
- Simulations parameterized without an adiponectin increase did not represent the clinical response

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