AASLD The Liver Meeting®

ACCURATE PREDICTION OF LIVER FAT REDUCTIONS ACROSS RANGE OF WEIGHT LOSS BY QUANTITATIVE SYSTEMS PHARMACOLOGY MODELING

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INTRODUCTION

Weight loss has positive effects on reducing hepatic lipid burden in MASH patients. Reports using various drugs have shown reductions of liver fat with weight loss[1-4]. Mechanistically, reduced food intake and weight loss lead to declines in adipose fatty acid (FA) release and hepatic de novo lipogenesis (DNL)[5,6]. NAFLDsym (Figure 1), a quantitative systems pharmacology (QSP) model[7], was used to characterize the relationship between weight loss and steatosis. The overall effects of weight loss on steatosis reductions in NAFLDsym were calibrated with data from clinical studies with liraglutide[1], canagliflozin[2], and retatrutide[3]. Simulation results were validated with clinical data from semaglutide studies[4]. Moreover, prospective predictions of weight loss[8] and liver fat reductions with tirzepatide were performed.

METHODS

A simulated cohort (SimCohorts) of 200 metabolic dysfunction-associated steatohepatitis (MASH) patients was included in simulations with NAFLDsym where daily caloric intake was adjusted from isocaloric amounts for each individual simulated patient. Clinically-observed weight loss was simulated by decreasing food intake (7%-30%) daily for 48 weeks; weight gain was simulated by increasing food intake (3%). Relative reductions in liver fat were predicted as a result of subsequent alterations in adipose FA release and hepatic DNL. Clinical data from liraglutide, canagliflozin, and retatrutide were used to calibrate the simulated steatosis changes. Clinical data from semaglutide studies were used to validate the simulation results. Predictions for tirzepatide were made by simulating its administration (5, 10, or 15 mg QW including uptitration). Exposures were directly simulated using a two compartment PK model. Simulated weight loss in the SimCohorts over 48 weeks agreed with clinical data; steatosis and fibrosis reductions were predicted.

RESULTS

Simulations of weight loss

- Weight loss due to caloric deficit via nutritional intervention was parameterized and simulated in OBESITYsym (Figure 2)
- OBESITYsym parameters for simulated weight loss were utilized within NAFLDsym predictions in MASH patients

Effect of weight loss on steatosis

- Simulations captured reductions in liver fat with weight loss, in alignment with clinical data from several drugs that elicit weight loss (Figure 3)
- Predicted relationship between weight loss and liver fat is linear between 5-15% weight loss, and it plateaus between 15-30% weight loss
- Predicted effects of tirzepatide on weight loss and liver fat reduction also aligned with the simulation results generated via consistent daily caloric reduction

Effect of weight loss on fibrosis stage

- Simulated weight loss predicted reductions in fibrosis stage in alignment with clinical data (Figure 4)

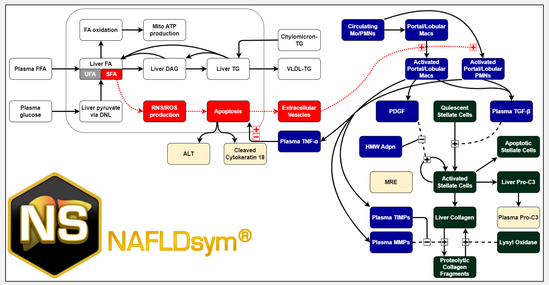

Figure 1. Diagrammatic illustration of MASH pathophysiology represented with NAFLDsym v2A. The mechanistic QSP model includes steatosis, lipotoxicity, inflammation, and fibrosis.

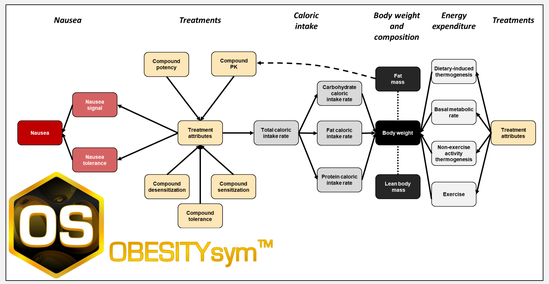

Figure 2. Diagrammatic illustration of OBESITYsym v1. The model simultaneously predicts the effects of drugs on food intake and/or energy expenditure as well as influencing sensitivity and/or tolerance to nausea.

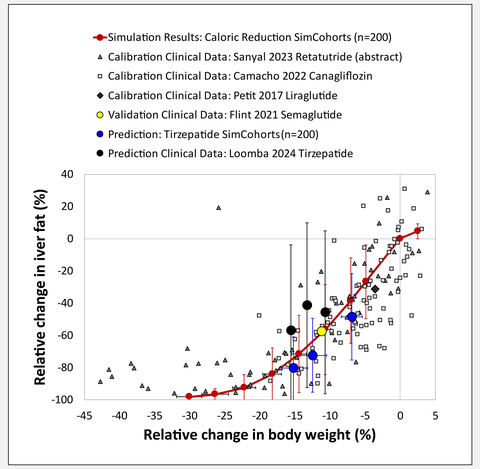

Figure 3. The quantitative relationship between weight loss and liver fat reductions in MASH patients, as expressed with both NAFLDsym simulation results (red, yellow, blue) and clinical data (grayscale). Clinical data from retatrutide, canagliflozin, and liraglutide studies were used to calibrate the quantitative relationship within NAFLDsym, while clinical data from a semaglutide study was used to validate the simulation. Predictions of steatosis reductions with tirzepatide treatments (5, 10, 15 mg QW, with uptitration) align with clinical data.

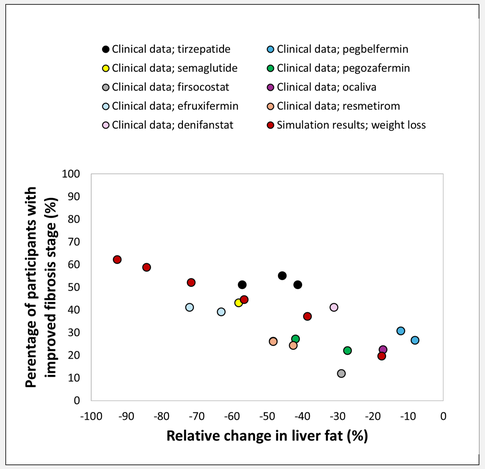

Figure 4. The quantitative relationship between liver fat reductions and fibrosis stage improvements in MASH patients, as expressed with both NAFLDsym simulation results and clinical data. The clinical data from tirzepatide, semaglutide, firsocostat, efruxifermin, denifanstat, pegbelfermin, pegozafermin, ocaliva, and resmetirom studies are included in the same plot as the simulated percentage of participants with improved fibrosis stage. As described in the Methods section, the simulated liver fat reductions were due to weight loss to varying extents. The alignment of clinical data and simulation results provides confidence in the ability of NAFLDsym to predict changes in fibrosis in addition to steatosis.

CONCLUSIONS

- OBESITYsym provides the ability to predict effects of drugs on weight loss
- NAFLDsym successfully represents the effects of weight loss via treatment on reducing liver fat and fibrosis in MASH patients
- Weight loss in excess of 10% has substantial, positive effects on reducing hepatic lipid burden, steatosis, and fibrosis in MASH patients
- This mechanistic modeling approach can be used to evaluate efficacy of weight loss drugs in MASH patients, either alone or in combination with other therapeutic approaches

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