Reduction of daily moderate alcohol intake predicted to decrease fibrosis stage in patients with non-alcoholic steatohepatitis

Christina Battista[1], James J Beaudoin[1], Kyunghee Yang[1], Scott Q Siler[1]

[1]DILIsym Services Division, Simulations Plus Inc., Research Triangle Park, NC

CONTACT INFORMATION: scott.siler@simulations-plus.com

BACKGROUND

Several recently completed clinical trials in NASH patients have included fibrosis stage reductions in 20-30% of the patients in placebo cohorts[1,2,3]. The mechanisms driving these reductions have not yet been identified. Reductions of alcohol (EtOH) intake could be influential, as moderate EtOH intake has been shown to enhance hepatic de novo lipogenesis[4]. Moreover, EtOH consumption is common in populations worldwide and has increased in some populations during the COVID-19 pandemic[5,6]. NASH clinical trial protocols do not exclude moderate EtOH consumers (20-30 g/d, equivalent to 1.5-2 standard drinks/d). A quantitative systems pharmacology (QSP) model, NAFLDsym[7] (Figure 1), was employed to test the hypothesis that reductions in daily moderate EtOH intake could reduce liver lipid burden, lipotoxicity, and fibrosis stage in NASH patients (Figure 2).

METHODS

NASH SimCohorts (Table 1) regularly consuming 30 or 15 g/d EtOH were used to simulate reductions in daily EtOH intake. Baseline EtOH administration was simulated as one or two 15 g drinks over one hour (Figure 3), coincident with the dinner meal. EtOH consumption at these levels were simulated for 1 year in the SimCohorts before subsequent reductions in intake were simulated. GastroPlus was used to simulate the rate of hepatic EtOH metabolism. Consistent with previous reports, 20% of the metabolized EtOH was able to contribute to hepatic de novo lipogenesis in the simulations[4,8]. Reductions of EtOH intake to 15 g/d or 0 g/d were simulated for 52 weeks in the 30 g/d SimCohorts (Figure 4). Similarly, the 15 g/d SimCohorts were used to simulate 0 g/d of EtOH intake (Figure 5). Changes in de novo lipogenesis, liver fat, plasma ALT, NAS, and fibrosis stage were predicted. Body weight did not change.

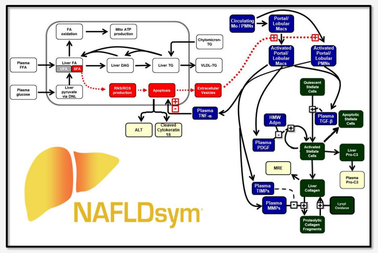

Figure 1. Diagrammatic illustration of NASH pathophysiology represented with NAFLDsym v2A. This includes steatosis, lipotoxicity, inflammation, and fibrosis.

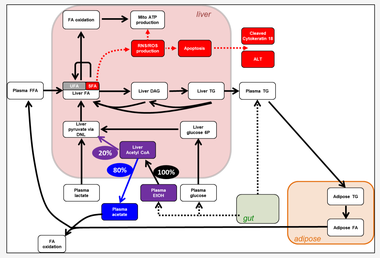

Figure 2. Representation of hepatic EtOH removal and intersection with de novo lipogenesis. This figure illustrates the uptake, metabolism, and partitioning of EtOH within the liver. Previous reports have indicated that 80% of metabolized EtOH exits the liver[4,8].

	EtOH 30 g, 7 d	EtOH 15 g, 7 d
Body weight (kg)	94.9 ± 18.4	94.9 ± 18.4
Liver fat (%)	20.7 ± 7.4	20.3 ± 7.1
Plasma ALT (U/L)	45.4 ± 13.4	44.7 ± 12.7
NAS	4.5 ± 1.2	4.5 ± 1.2
Fibrosis stage	2.6 ± 0.5	2.5 ± 0.5
Average 24 h de novo lipogenesis	1.83 ± 0.32	1.30 ± 0.28

Table 1. Characteristics of the SimCohorts. Simulated patients (n=140) regularly consumed 30 g EtOH, 7 d/wk or 15 g EtOH, 7 d/wk prior to simulated reductions in EtOH intake.

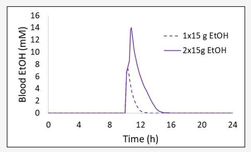

Figure 3. Simulated blood alcohol levels. GastroPlus was used to predict blood alcohol levels after 1 drink (1x15 g EtOH) or 2 drinks (2x15 g EtOH) within 1 hour. In simulations, EtOH consumption was coincident with the third meal of the day (t=10h).

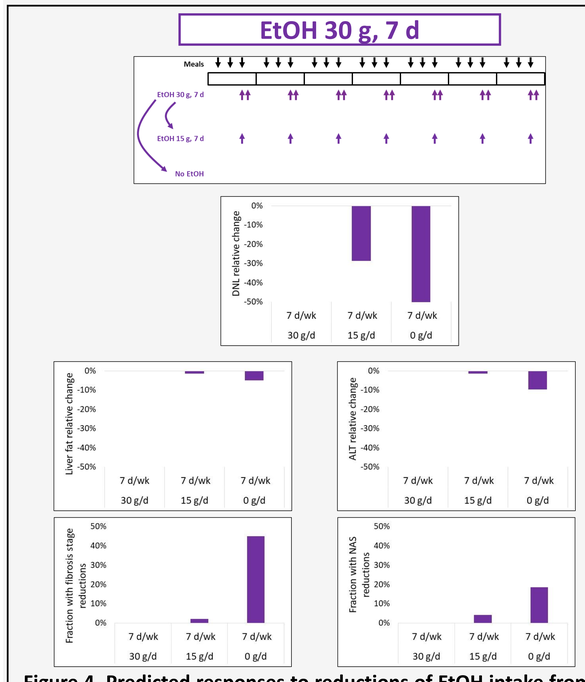

Figure 4. Predicted responses to reductions of EtOH intake from 30 g/d to 15 g/d or 0 g/d. SimCohorts adjusted EtOH intake in simulations to reduce the total consumed amount per day. No weekly EtOH intake was also simulated.

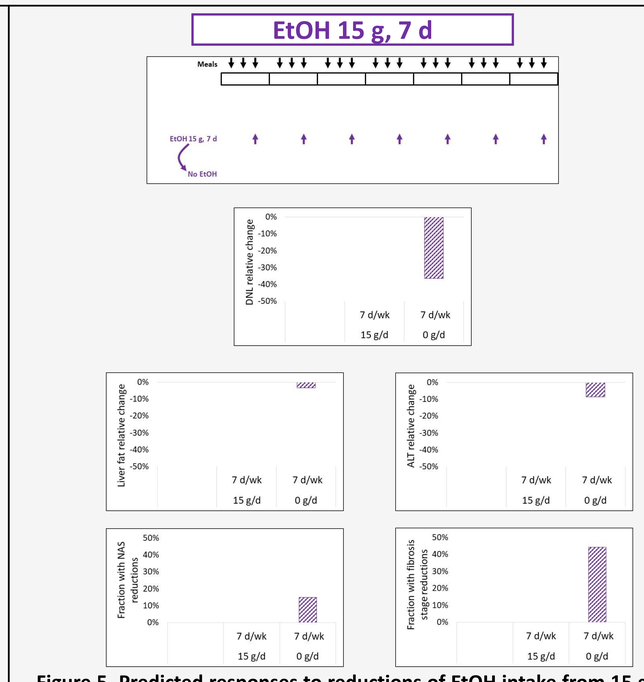

Figure 5. Predicted responses to reductions of EtOH intake from 15 g/d to 0 g/d. SimCohorts adjusted EtOH intake in simulations to reduce the total consumed amount per day. No weekly EtOH intake was also simulated.

RESULTS

Decreased EtOH intake elicited fibrosis stage and NAS reductions in the SimCohorts originally consuming 30 g/d, with a greater proportion of patients with an improved fibrosis stage in the 0 g/d vs. 15 g/d simulations (Figure 4). Twenty-four-hour average de novo lipogenesis was predicted to decline in the 0 g/d or 15 g/d simulations. Modest reductions in liver fat and ALT were predicted when EtOH intake was reduced to 0 or 15 g/d. Similar changes were predicted as SimCohorts transitioned from consuming 15 g/d to 0 g/d (Figure 5).

CONCLUSION

Reductions in moderate EtOH intake for NASH patients who are regular consumers may lead to improvements in fibrosis stage due to decreased de novo lipogenesis. This behavioral adjustment may influence the frequency of observed fibrosis stage reductions in clinical trials whether on placebo or treatment, particularly in studies conducted in regions with a higher prevalence of moderate EtOH consumption.

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