Predicting the safety and efficacy of inhibition of diacylglycerol transferase 2 for the treatment of non-alcoholic fatty liver disease
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Objective: With no effective treatment, non-alcoholic fatty liver disease (NAFLD) decreases patient quality of life and leads to increased healthcare costs. Here we assess the efficacy and safety of a novel approach to reversing hepatic steatosis, inhibition of diacylglycerol transferase 2 (DGAT2). We utilized a systems pharmacology approach to test if we should expect a better clinical benefit for NAFLD from DGAT2 inhibitors versus their metabolic “next-door neighbors” in VLDL synthesis: microsomal triglyceride transfer protein (MTP) inhibitors. While MTP inhibitors have previously been reported to cause lipotoxicity in the liver (1), preclinical data indicate that DGAT2i may not (2).

Methods: We utilized DILIsym, a systems pharmacology model of liver metabolism to represent NAFLD pathophysiology, including liver triglyceride synthesis, storage, and release as VLDL and effects of lipotoxicity on hepatocellular health (3). We simulated MTP and DGAT2 inhibition to differentiate their effects on liver TG and hepatocellular apoptosis. We tested the pharmacodynamics of the DGAT2 inhibitor with and without reported gene expression changes in fatty acid synthesis, esterification, and oxidation (2).

Results: In contrast to the MTP inhibitor, the DGAT2 inhibitor was predicted to reduce liver triglycerides (up to 90%), without exacerbating lipotoxicity. MTP, however, elicited increases in liver TG and lipotoxicity. Performing a sensitivity analysis on the pharmacodynamics of the DGAT2 inhibitor demonstrated that adaptations by fatty acid uptake pathway were the most important to minimize lipotoxicity.

Conclusions: A systems pharmacology model has provided insight into DGAT2 inhibition as a strategy for the treatment of NAFLD and established its differentiation from the failed MTP inhibitors. However, the predicted patient response is sensitive to critical adaptive responses and should be verified in follow-on studies.

References: