PS-109

Partial inhibition of de novo lipogenesis with the acetyl-CoA carboxylase inhibitor PF-05221304 does not increase circulating triglycerides in humans and is sufficient to lower steatosis in rats

William Esler[1], Trenton Ross[1], Arthur Bergman[1], Collin Crowley[1], Santos Carvajal Gonzalez[1], David Beebe[1], Jeffrey A Pfefferkorn[1], Neeta Amin[1]

[1]Pfizer Worldwide Research and Development, Cambridge Massachusetts, United States

Email: william.esler@pfizer.com

Background and aims: Increased hepatic de novo lipogenesis (DNL) and reduced fatty acid oxidation are hypothesized to contribute to steatosis and lipotoxicity in non-alcoholic steatohepatitis (NASH). Acetyl-CoA carboxylase (ACC) catalyzes the first step in DNL, and modulates mitochondrial fatty acid oxidation. Inhibition of ACC by MK-4074 was shown to inhibit DNL and reduce steatosis in patients with NAFLD along with unexpected increases in circulating triglyceride (TG) levels (*Cell Metab.* 2017;26:576). That study evaluated a dose of MK-4074 which fully inhibited hepatic DNL. We sought to determine if partial inhibition of hepatic DNL with the liver-targeting ACC inhibitor PF-05221304 could decouple DNL inhibition from circulating TG elevations in rats and humans.

Method: The dose-response for hepatic DNL inhibition, circulating TG levels and steatosis was evaluated following administration of PF-05221304 for 4 weeks in Western-diet-fed rats. The dose response for hepatic DNL inhibition and serum TG levels was also evaluated in healthy adult humans administered oral PF-05221304 or matching-placebo for 14 days.

Results: Administration of PF-05221304 to healthy adult humans inhibited hepatic DNL in a dose-dependent manner, with a maximum average inhibition of 98%. At doses of PF-05221304 sufficient to inhibit DNL by > 90%, fasting and 24 hour serum TG levels were increased relative to baseline. However, increases in serum TG levels were not observed at doses which inhibited hepatic DNL by an average of ≤ 80%. To determine if doses which partially inhibit hepatic DNL are sufficient to reduce steatosis, studies were conducted in Western-diet-fed rats. Oral administration of PF-05221304 at 1, 3, and 10 mg/kg to Western-diet-fed rats inhibited hepatic DNL by 47%, 58% and 73% respectively relative to vehicle ($p < 0.001$). Mean reduction in steatosis of 60% ($p < 0.0001$) at the 2 higher doses were observed despite only partially inhibiting hepatic DNL.

Conclusion: Doses of PF-05221304 which only partially inhibit hepatic DNL (≤ 80% inhibition) did not elevate fasting or 24 hour serum TG levels in adult humans. Partial inhibition of hepatic DNL (58% and 73%) was sufficient to robustly lower steatosis in Western-diet-fed rats. Additional studies are needed to determine if these findings translate to patients with NASH.

Figure:

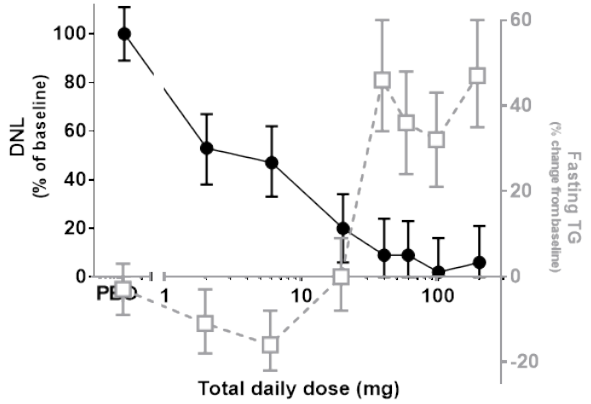

Figure 1: Dose-response relationship for hepatic DNL inhibition (% of baseline; mean ± 90% confidence interval) and % change from baseline (mean ± 80% confidence interval) in fasting serum triglyceride levels in healthy adult humans.