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The glucocorticoid antagonist ST001 prevents development of NASH and improves aspects of the metabolic syndrome in the DIAMOND (TM) mouse model

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Background and aims: The steroid ST001 (fluasterone, SteroTherapeutics) is a strong in vivo antagonist to glucocorticoids that retains beneficial immunosuppressive effects. It is being evaluated as a treatment for Cushing's Syndrome, in which most patients are insulin resistant and obese and 20% develop NASH. We aimed to determine if ST001 could prevent development of NASH in the DIAMOND™ mouse model.

Method: Mice were randomized into 4 groups: high dose (HD 20 mg/kg), low dose (LD 5 mg/kg), WDSW positive (PC) and NCNW negative (NC) natural history controls. Mice were raised for 16 weeks on diet, corresponding to a baseline NASH with mild fibrosis in all WDSW groups. Treatment groups were then injected once daily with aqueous vehicle or drug in vehicle for the 16 wks they were on-diet. Serum biomarkers of insulin sensitivity, LFTs, lipids, and liver histology (HandE and Sirius Red) were assessed.

Results: At necropsy, the body weight and liver weight of the mice in the HD group were significantly lower than the PC and LD groups. Interestingly, steatosis percentage was higher in the fluasterone-dosed groups compared to PC, but steatosis grade did not differ. Fasting blood glucose was higher in the treated groups, but ketones and serum triglycerides were lower compared to PC. No statistically significant differences in serum insulin or HOMA-IR were observed, although there was a strong trend to lower insulin in the HD group. Serum LFTs and cholesterol did not differ between the PC and treatment groups. Fluasterone had significant anti-fibrotic effects; NASH CRN fibrosis scores were significantly lower in both treatment groups compared to WDSW positive controls ($P \leq 0.001$) and perisinusoidal fibrosis was also significantly lower in both treatment groups ($P \leq 0.01$). While 66% of the 16-wk positive control mice progressed to NASH, none of the mice being treated with fluasterone progressed beyond simple steatosis, and this lack of progression was highly statistically significant ($P \leq 0.001$). Fluasterone eliminated ballooning in both dose groups compared to PC ($P \leq 0.0001$). Lobular inflammation and NAS score did not differ between groups but the SAF activity score was lower in both dose groups.

Conclusion: Fluasterone successfully met the primary study end point of preventing NASH development. While not an insulin sensitizer, it did improve some measures of insulin sensitivity and metabolic syndrome, suggesting that the development of NASH in this model may be partly driven by glucocorticoids as with Cushing's disease. These results support the biological rationale for further testing of anti-glucocorticoid compounds with immunosuppressive effects like fluasterone as NASH therapeutics.

Figure: