IVA337, A PAN-PPAR AGONIST, REDUCES NAS AND INHIBITS THE INFLAMMASOME IN MURINE MODELS OF NAS

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a complex liver pathology starting from simple hepatocellular steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and ultimately cirrhosis. We have already reported that IVA337, a well-balanced pan-PPAR agonist, currently in phase 2b, reduces body weight gain, serum triglycerides, adiposity index and insulin resistance in a Diet Induced Obesity (DIO) model. IVA337 also prevented and reversed liver fibrosis in a CCl4 model. Inflammation has been described to be activated in NASH patients and to contribute to the development of the disease (obesity, IR) as well as fibrosis.

We aimed to evaluate the effect of IVA337 in two mechanistically different models of NASH (MCD and foz/foz) and to study its effect on crucial pathways implicated in NASH and fibrosis development.

RESULTS

IVA337 activity on NASH parameters in the foz/foz model

- IVA337 decreases steatosis, ballooning and inflammation compared to control group
- All animals in the HFD groups have a NAS ≥ 5. Only 1 animal has a NAS = 5, all the other have a NAS ≤ 4 in the IVA337 30mg/kg treated group
- IVA337 improves all the overall NASH features

2-MATERIAL/METHODS

- C57Bl/6 mice were fed for 3 weeks with Methionine-Choline deficient diet (MCD) diet and simultaneously treated with IVA337
- Foz/foz mice received HFD for 6 weeks to initiate NASH pathology and were kept under HFD alone or in combination with IVA337 for another 6 weeks.
- Besides biological and histological markers, gene expression analysis was performed on liver lysate of these two experiments.

CONCLUSION

These findings demonstrate that IVA337 inhibits the development of NASH through the normalization of different metabolic parameters such as insulin-resistance but also through activation of P-oxidation, decrease in liver toxicity and inhibition of the inflammasome known to be a trigger of liver inflammation and fibrosis.