IVA337, A PAN-PPAR AGONIST, REDUCES NASH FEATURES AND INHIBITS THE INFLAMMASOME IN MURIN MODELS OF NASH

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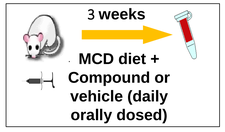
1-INTRODUCTION

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. Inflammasome has been described to be activated in NASH patients and to contribute to the development of the disease (obesity, IR) as well as fibrosis.

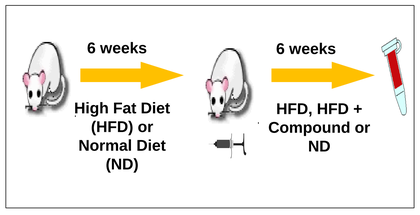
We aimed to evaluate the effect of IVA337 in two mechanistically different models of NASH (MCD and foz/foz) and to study its effect on crucial pathways implicated in NASH and fibrosis development.

2-Material/Methods

- C57bl/6 mice were fed for 3 weeks with Methionine-Choline deficient (MCD) diet and simultaneously treated with IVA337



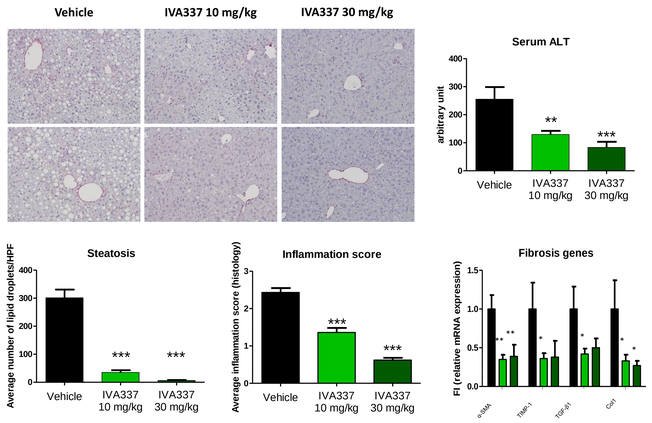
- Foz/foz mice received HFD for 6 weeks to initiate NASH pathology and were kept under HFD alone or in combination with IVA337 for another 6 weeks.



- Besides biological and histological markers, gene expression analysis was performed on liver lysate of these two experiments.

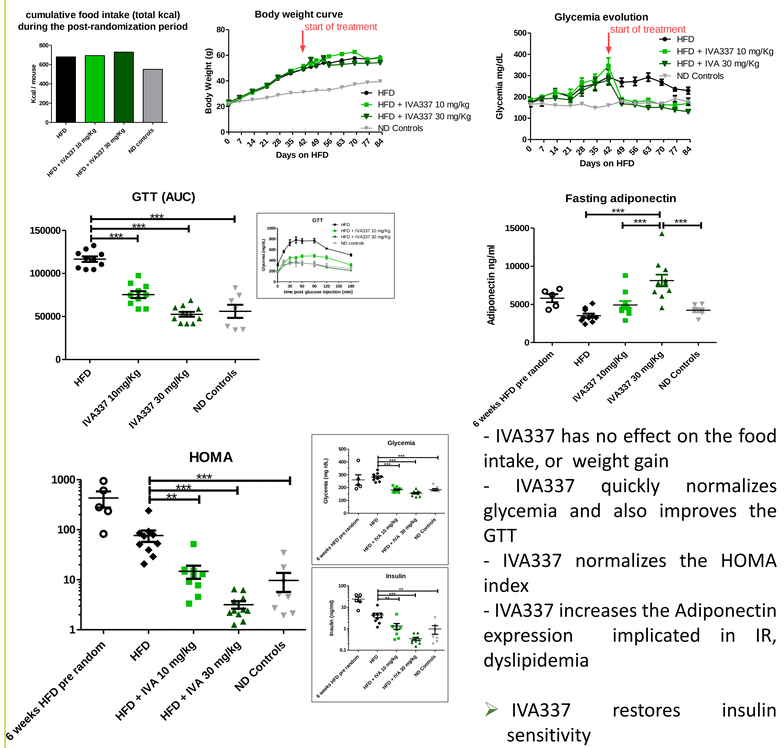
3-RESULTS

IVA337 activity in Methionine-Choline deficient diet model



➢ IVA337 inhibits steatosis, inflammation, fibrotic genes expression and improves global liver condition

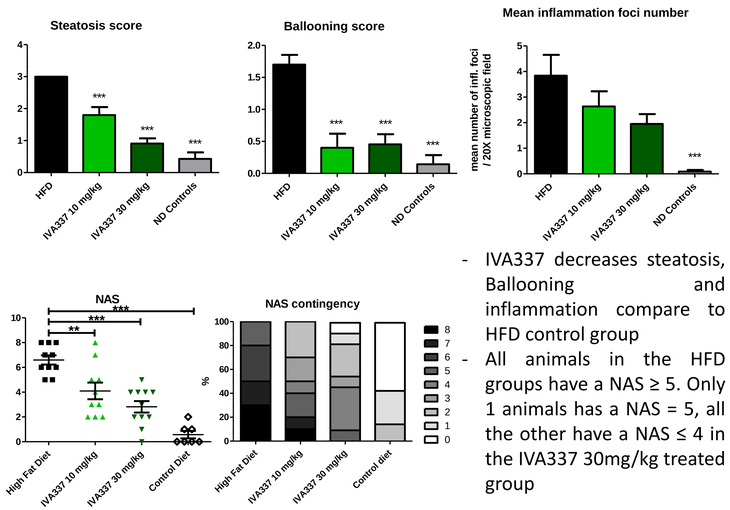
IVA337 activity on glycemia and adiponectin in the foz/foz model



- IVA337 has no effect on the food intake, or weight gain
- IVA337 quickly normalizes glycemia and also improves the GTT
- IVA337 normalizes the HOMA index
- IVA337 increases the Adiponectin expression implicated in IR, dyslipidemia

➢ IVA337 restores insulin sensitivity

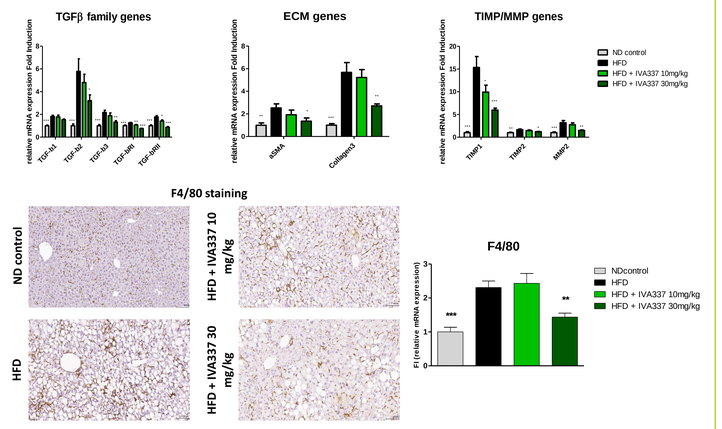
IVA337 activity on NASH parameters in the foz/foz model



- IVA337 decreases steatosis, Ballooning and inflammation compare to HFD control group
- All animals in the HFD groups have a NAS ≥ 5. Only 1 animals 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

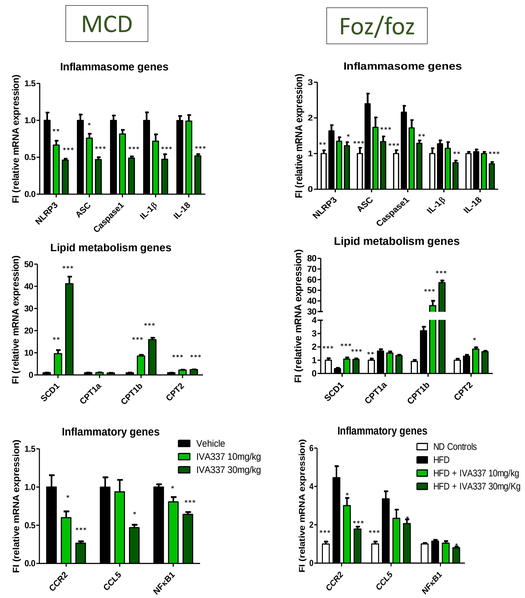
IVA337 activity on fibrosis in the foz/foz model



- IVA337 decreases fibrotic genes expression
- HFD control groups demonstrates an increase in macrophages recruitment that is abolished with IVA337 treatment

➢ IVA337 improves liver fibrosis induced by HFD in foz/foz model

IVA337 activity on inflammasome, lipids metabolism and inflammation related genes expression in MCD and foz/foz model



- IVA337 decreases the expression of all the inflammasome components in both models
- IVA337 activates in the two models the expression of CPT1b and CPT2 that are involved in the β-oxidation
- SCD1, that is involved in the monodesaturation of saturated fatty acids (producing cell toxicity and inflammation) is up regulated by IVA337 in MCD and normalized in foz/foz
- IVA337 decreases the expression of inflammatory factors such as CCR2, CCL5 and NFκB

➢ IVA337 demonstrates positive effects regarding the pathways that are either activated or inhibited during NASH development

4-CONCLUSION

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