SAFETY AND EFFICACY OF THE PAN-CASPASE INHIBITOR IDN-6556 ON THE TREATMENT OF NONALCOHOLIC FATTY LIVER AND INSULIN RESISTANCE

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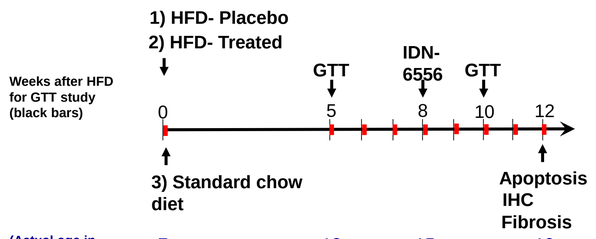
PURPOSE / AIM

- Hepatocellular and extrahepatic cell death are important features of obesity-associated fatty liver disease (NAFLD) and metabolic syndrome
- Inhibition of caspases may be a viable therapeutic approach for treatment
- Our **aim** was to test whether the pan-caspase inhibitor, IDN-6556, reverses hepatic steatosis and reduces metabolic abnormalities observed with NAFLD, such as insulin resistance and dyslipidemia

METHODS

- C57BL/6 mice, aged 6 to 8 weeks at the beginning of the study, were fed a high fat "western" diet (HFD) or a low fat, normal chow (NC), control diet for 12 weeks
- Starting on week 6 mice fed the HFD were subject to drug or placebo treatment for 5 weeks

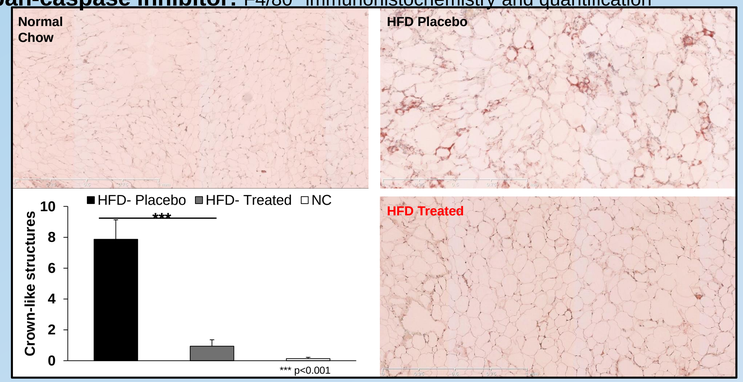
Experimental Design



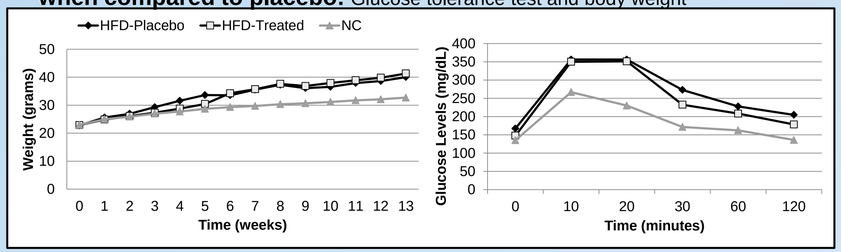
- Glucose tolerance tests (GTT) were performed at weeks 5 and 12
- Liver, blood, and adipose tissue were collected after week 12
- Insulin, glucose and triglyceride levels were measured, the lipid profile was assessed and adipose inflammation was examined

RESULTS

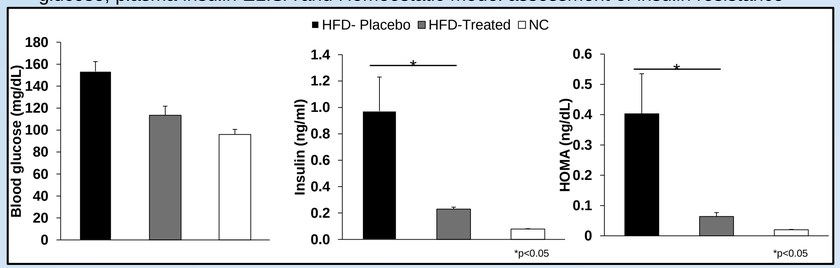
The number of crown-like structures was reduced in mice given the pan-caspase inhibitor: F4/80+ immunohistochemistry and quantification



Treated mice showed a decrease in terminal blood glucose levels when compared to placebo: Glucose tolerance test and body weight

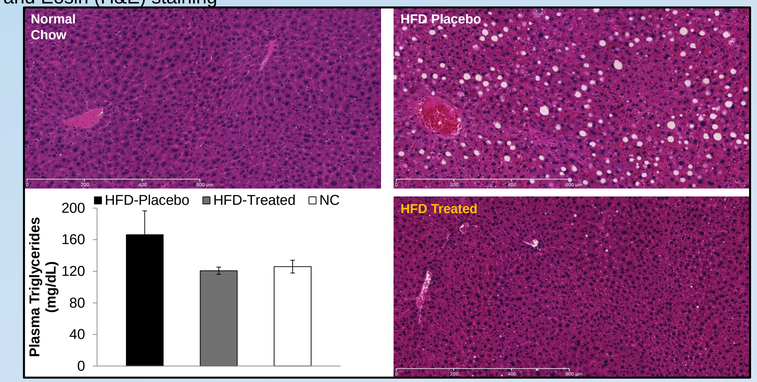


IDN-655 treatment resulted in improved insulin function: Terminal blood glucose, plasma insulin ELISA and Homeostatic model assessment of insulin resistance



RESULTS

Drug administration caused decreased hepatic steatosis: Hematoxylin and Eosin (H&E) staining



CONCLUSION

The data shown suggests that oral administration of the experimental drug IDN-6556 reduces adipose inflammation and resolves hepatic steatosis. In addition, fasting glucose and insulin levels decreased in the treated group. The findings indicate that IDN-6556 might be a promising method of therapy and warrants further research

FUNDING

This study was supported in part by an unrestricted grant from Conatus Pharmaceutical and NIH grant DK082451 to AEF

EASL THE INTERNATIONAL LIVER CONGRESS™ 2013
48th ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER
AMSTERDAM, THE NETHERLANDS, APRIL 24-28 / 2013