PAN-CASPASE INHIBITION PROTECTS AGAINST FIBROTIC NASH INDUCED BY CHOLINE DEFICIENT AMINO ACID DEFINED DIET (CDAA)

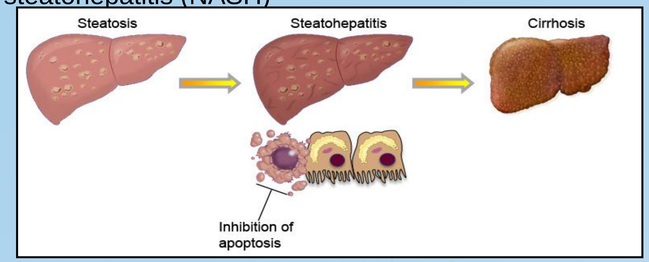
W. Lu[1], A. Eguchi[1], D. Sirbu[1], P. Contreras[2], C. Johnson[1], A. Wree[1], D. Povero[1], M. Lazic[1], and A. Feldstein[1]

[1]Pediatrics, University of California, San Diego, La Jolla, [2]Conatus Pharmaceuticals, San Diego, CA, USA.

UC San Diego MEDICAL CENTER

PURPOSE / AIM

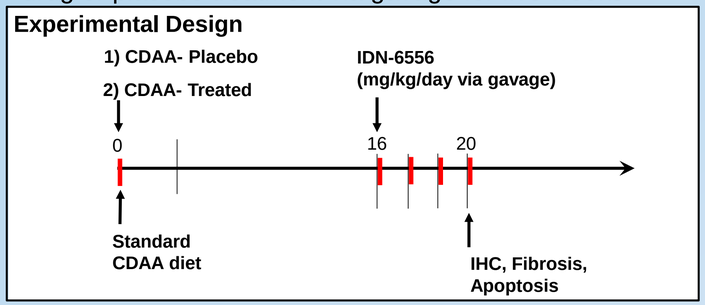
- Hepatocyte cell death is a key feature of nonalcoholic steatohepatitis (NASH)



- Emerging data suggests that inhibition of **caspases** may be an attractive therapeutic approach for patients with NASH
- Our **aim** was to determine if the pan-caspase inhibitor, IDN-6556, reduces hepatocellular apoptosis and fibrosis

METHODS

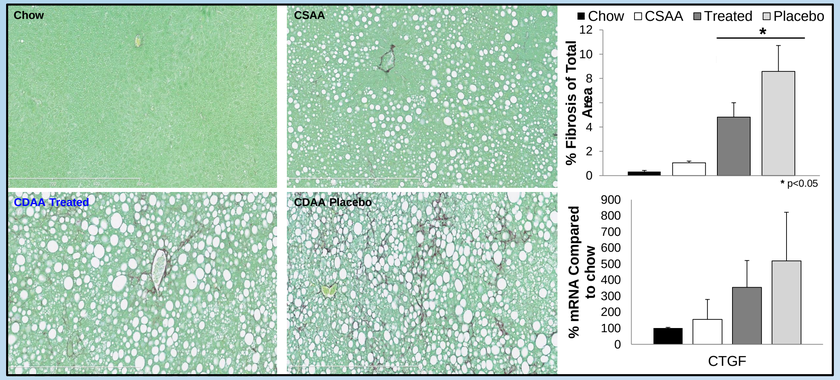
- C57BL/6 mice were fed a CDAA or a choline-sufficient amino acid-defined (CSAA) diet for 20 weeks
- Starting on week 16, mice fed the CDAA diet were subject to drug or placebo treatment via gavage for five weeks



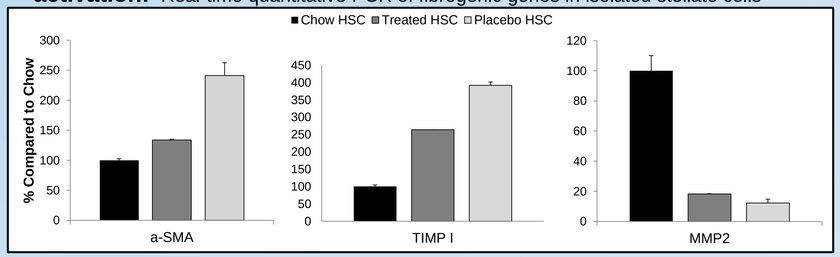
- Liver and blood were collected after week 20
- Hepatocellular apoptosis, fibrosis and inflammatory activity were assessed

RESULTS

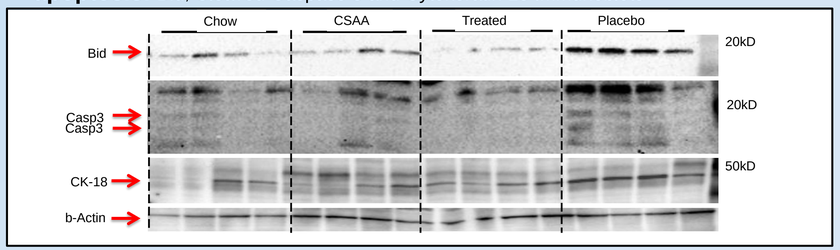
Liver Fibrosis was diminished in treated mice: Sirius Red quantification and expression of CTGF mRNA



IDN-6556 administration reduced Hepatic Stellate Cell (HSC) activation: Real-time quantitative PCR of fibrogenic genes in isolated stellate cells

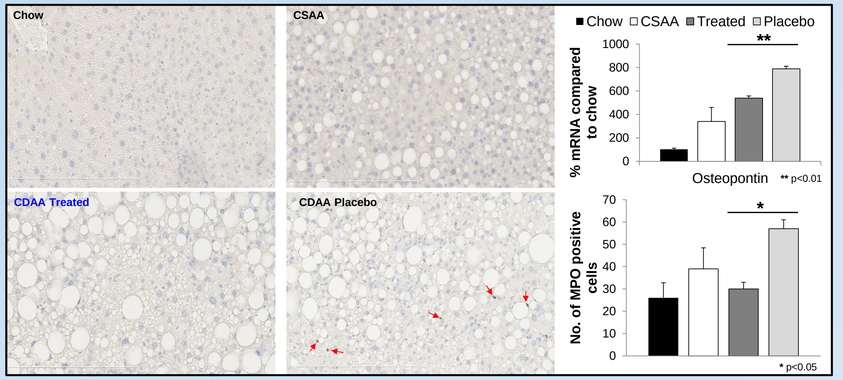


Mice that received the pan-caspase inhibitor showed inhibition of apoptosis: Bid, Cleaved Caspase 3 and Cytokeratin 18 Immunoblots



RESULTS

Neutrophil infiltration in the liver declined after exposure to the drug: Myeloperoxidase (MPO) Staining and Osteopontin mRNA Expression



CONCLUSION

The data shown suggests that oral administration of the experimental drug IDN-6556 inhibits apoptosis and attenuates fibrosis and inflammation associated with experimental NASH. ALT/AST levels (not shown) showed no marked decrease between CDAA treated and CDAA placebo groups, while Insulin levels (not shown) showed a significant decrease in the treated group. The findings indicate that IDN-6556 might be a promising method of therapy and warrants further research

FUNDING

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