The Farnesoid X Receptor (FXR) Agonist EDP-305 Reduces Ascites and Hepatocellular Carcinoma Development in a Rat Model of Cirrhosis

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Background: Farnesoid X Receptor

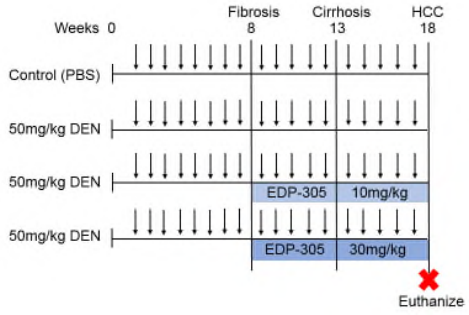
Farnesoid X receptor (FXR) is a nuclear receptor and a key regulator of bile acid homeostasis.

FXR agonists are currently under clinical investigation for the management of various liver diseases (i.e. primary biliary cholangitis and nonalcoholic steatohepatitis).

However, most preclinical studies have examined the effects of FXR agonists in models where the disease has not yet progressed to cirrhosis with its associated co-morbidities, including hepatic decompensation, hepatocellular carcinoma (HCC), and death.

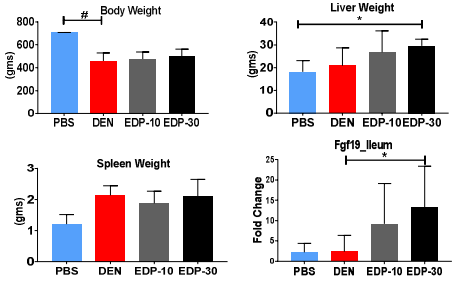
Here, we investigate the effects of the FXR agonist EDP-305 on these endpoints in a rat model of cirrhosis and HCC.

DEN-Induced Rat Model of Cirrhosis and HCC with EDP-305 Treatment

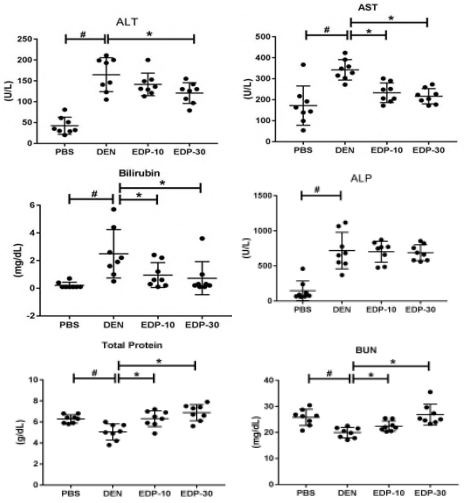


Male Wistar rats (n=10 in each group) received weekly intraperitoneal injections (as indicated by arrows) of either PBS or DEN for 18 weeks. In this model, fibrosis develops after 8 weeks, cirrhosis after 12 weeks, and HCCs after 15 weeks. EDP-305 was administered daily by oral gavage from weeks 9-18.

EDP-305 Treatment was Well Tolerated in the DEN Rat Model

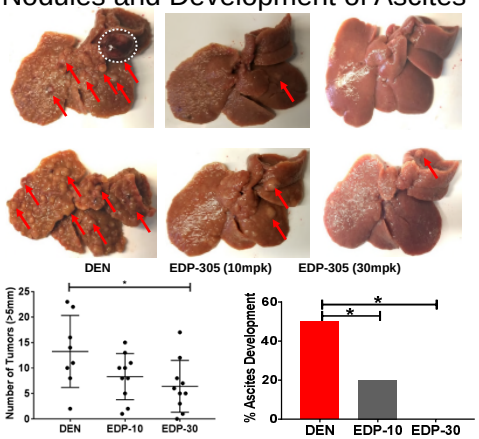


EDP-305 treatment was well tolerated in DEN-injured rats as indicated by no change in body weight. EDP-305 increased ileal Fgf19 gene expression indicative of FXR agonism.



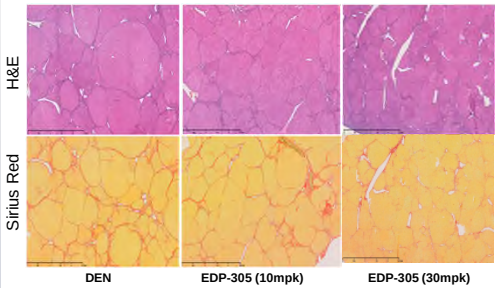
EDP-305 treatment dose-dependently decreased serum ALT and AST levels, as well as serum bilirubin levels, suggestive of reduced hepatic injury and cholestasis, respectively.

EDP-305 Treatment Reduced Tumor Nodules and Development of Ascites



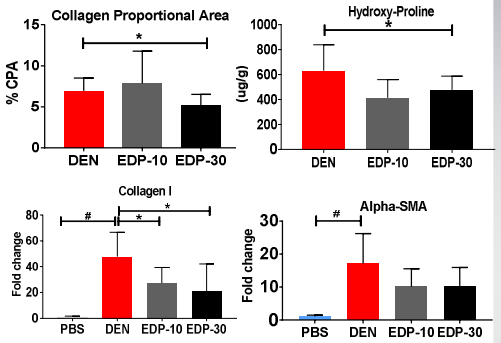
Representative gross pictures at the time of sacrifice. Arrows indicate tumors. 2 out of 10 DEN rats died before the end of the study. Of the remaining 8 rats, 4 developed ascites. All EDP-305-treated animals survived. 2 out of 10 animals in the EDP-305 10 mpk developed ascites whereas ascites was not observed in animals receiving EDP-305 30mpk.

EDP-305 Treatment Reduced Fibrosis



EDP-305 dose-dependently decreased fibrosis in DEN-injured rats as assessed by Sirius red staining.

EDP-305 Treatment Reduced Fibrosis



EDP-305 30 mpk reduced fibrosis as assessed by morphometric quantification of the collagen proportional area (CPA) in Sirius Red stained liver sections and HPLC measurement of Hydroxy-Proline levels in liver tissue. qPCR further confirmed reduced expression of *Col1A1* and *Acta2* after treatment.

Conclusion

In a rat model of cirrhosis and HCC, EDP-305 reduced:

- Serum markers of liver injury
- Fibrosis
- Ascites development
- HCC development
- Mortality

EDP-305 might be effective in patients with late stage (F3-F4) fibrotic liver disease.