

The pan caspase inhibitor emricasan improves the hepatic microcirculatory dysfunction of CCl₄-cirrhotic rats leading to portal hypertension amelioration and fibrosis reduction

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Background and aims

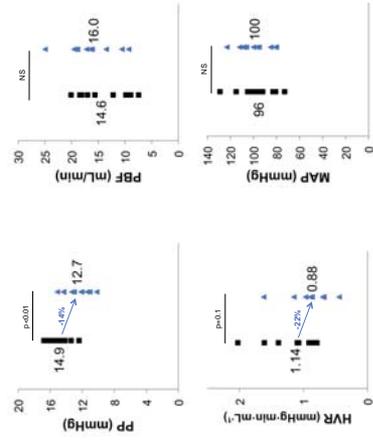
In cirrhosis, liver microvascular dysfunction is the key factor increasing hepatic vascular resistance (HVR) to portal blood flow that leads to portal hypertension. De-regulated inflammatory and pro-apoptotic processes due to chronic injury play a key role in the dysfunction of liver sinusoidal endothelial and hepatic stellate cells (LSEC & HSC). The present project aimed at characterizing the effects of the pan-caspase inhibitor emricasan on the systemic and hepatic hemodynamic, and LSEC & HSC-phenotype in a pre-clinical model of advanced chronic liver disease.

Methods

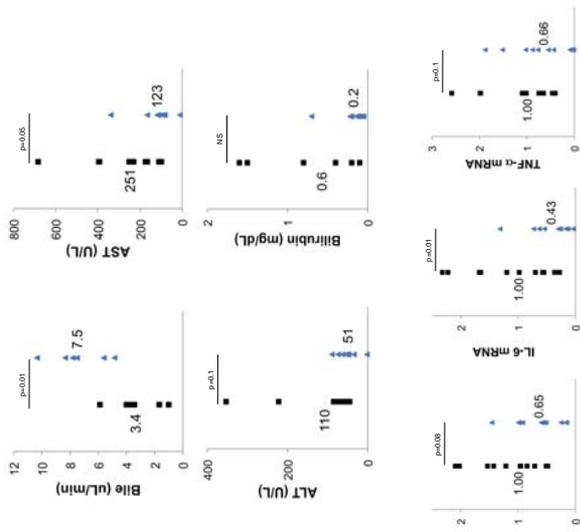
CCl₄-cirrhotic rats received emricasan (10mg/kg/day, i.p.) or vehicle (carboxymethylcellulose) for 7 days (n=12 per group). Measurements: *in vivo* systemic and hepatic hemodynamic (mean arterial pressure, MAP; portal pressure, PP; portal blood flow, PBF; and HVR), liver function & injury (bile production, AST, ALT, bilirubin), hepatic microcirculatory function (portal perfusion pressure [PPP] response to incremental doses of acetylcholine), inflammation (IL-1 β , IL-6 & TNF- α), fibrosis (Sirius red staining & collagen) and phenotype of LSEC (eNOS, fenestrate porosity) & HSC (α -SMA, and rho kinase [p-moesin/moesin]).

Results

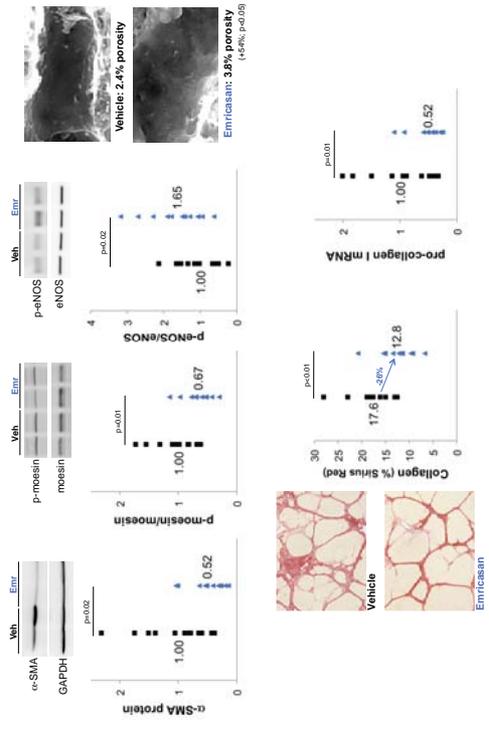
1- Hepatic and systemic hemodynamic



2- Liver function, injury and inflammation



3- HSC & LSEC phenotype - Fibrosis



Cirrhotic rats receiving emricasan exhibited improved HSC phenotype (α -SMA and Rho kinase) and LSEC phenotype (p-eNOS and fenestrate porosity), which led to significant reduction on liver fibrosis (Sirius Red and collagen I).

Conclusions

- Emricasan improves liver sinusoidal microvascular dysfunction in a pre-clinical model of advanced cirrhosis, which leads to marked amelioration in fibrosis, portal hypertension and liver function.
- These results encourage its clinical evaluation in the treatment of advanced chronic liver disease.

Emricasan-treated cirrhotic animals exhibited better liver function and less liver injury (bile production, transaminases release and bilirubin), which was accompanied by marked anti-inflammatory effects.

Top, cirrhotic rats receiving emricasan showed significantly lower PP due to a reduction in HVR. No systemic effects were observed.
Bottom, endothelial dysfunction improvement in animals receiving emricasan.