Emricasan, a pan caspase inhibitor, improves survival and portal hypertension in a murine model of common bile-duct ligation

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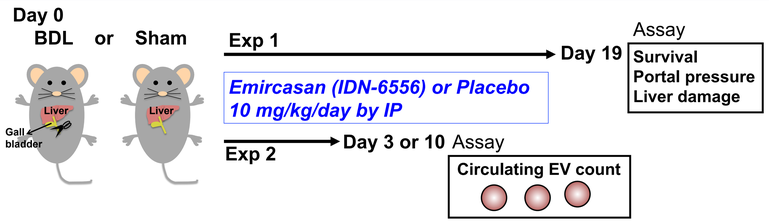
PURPOSE / AIM

- ★ Development of portal hypertension (PTH) is a central prognostic factor in patients with cirrhosis. Current pharmacotherapy remains limited and novel therapies are greatly needed.
- ★ Circulating extracellular vesicles (EVs) are released by hepatocytes in a caspase dependent manner, are increased in circulation of patients with cirrhosis and contribute to PTH via induction of impaired vasoconstrictor responses
- ★ We tested the hypothesis that Emircasan (IDN-6556) a pan-caspase inhibitor ameliorates PTH via its anti-fibrotic effects and reduction in release of EVs.

METHODS



RESULTS

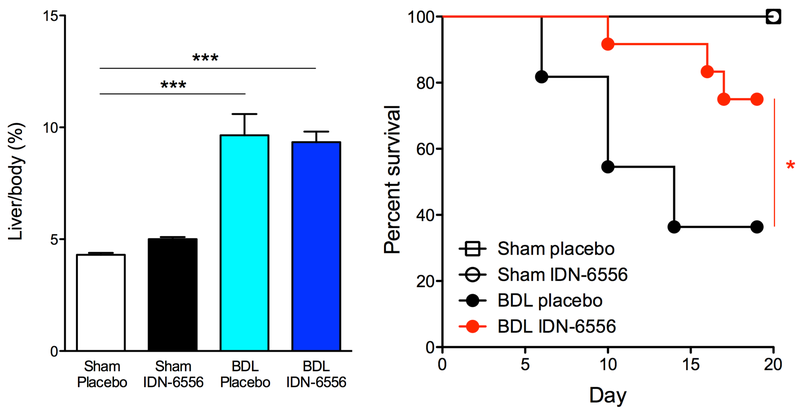


Figure 1. Liver/body ratio and survival curve: The liver/body ratio was significantly increased in BDL group compared to Control group (p<0.001), but no difference between CBDL-Placebo group and CBDL-IDN-6556 group. Nearly all CBDL-IDN-6556 survived compared to CBDL-Placebo group (p<0.05). [*** p<0.001, * p<0.05]

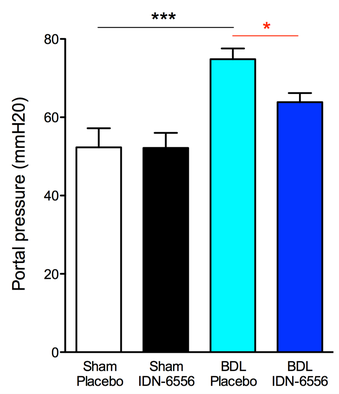


Figure 2. Portal pressure: Assessment of portal pressure showed a significant increase in CBDL-placebo treated mice compared to sham-operated mice (p<0.001).
In contrast, CBDL-IDN-6556 treated mice had significantly lower levels than CBDL-Placebo treated animals (p<0.05).
[*** P<0.001, * P<0.05]

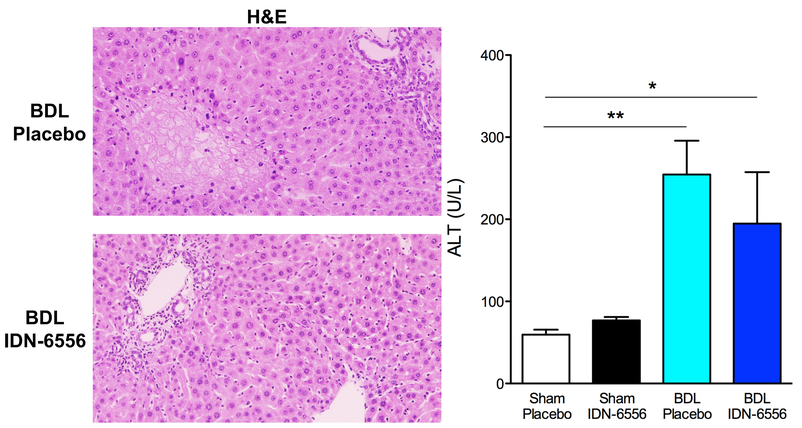


Figure 3. Liver histology and ALT: Analysis of liver injury showed that CBDL-IDN-6556 treated mice had improved liver histology stained by H&E. Serum ALT levels showed an decreasing trend in CBDL-IDN-6556. [** p<0.01, * p<0.05]

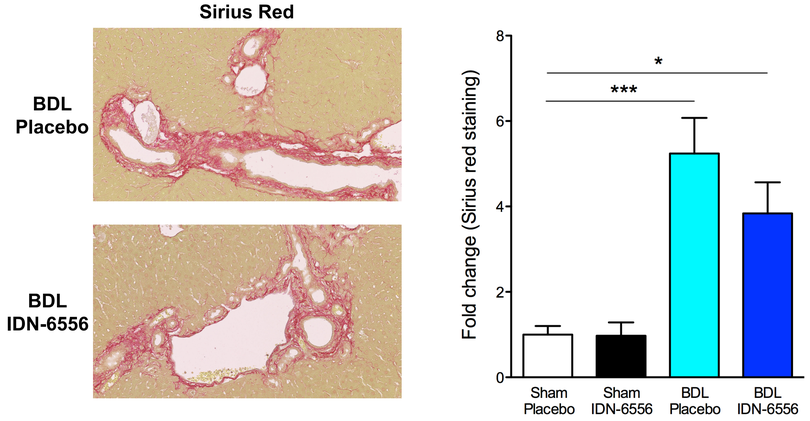


Figure 4. Liver fibrosis: IDN-6556 treatment resulted in a decrease in fibrosis, but the changes did not reach statistical significance suggesting that the effects on PTH are at least in part independent of the anti-fibrotic effects of the drug. [*** p<0.001, * p<0.05]

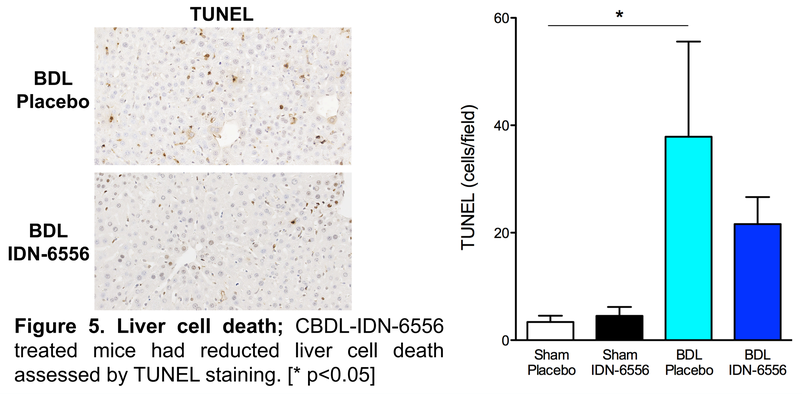


Figure 5. Liver cell death; CBDL-IDN-6556 treated mice had reducted liver cell death assessed by TUNEL staining. [* p<0.05]

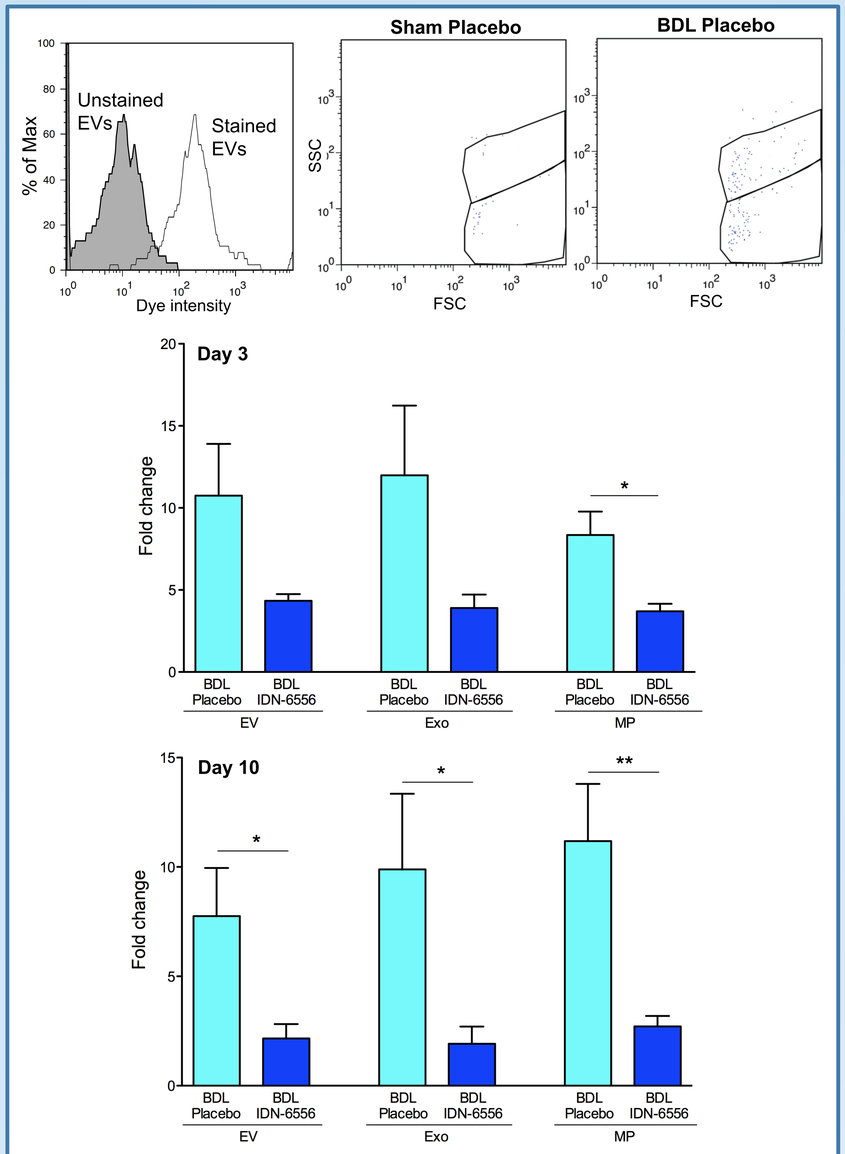


Figure 6. Circulating EVs in blood via flow cytometry: Circulating EVs were quantified using calcein positive EVs (histogram). Circulating EVs were increased in CBDL and had two populations (exo: exosomes and MP: microparticles) (dot plot). IDN-6556 treatment resulted in a significant decrease in circulating MPs at Day 3 (p<0.05) and at Day 10 (p<0.01). [** P<0.01, * P<0.05]

CONCLUSIONS

These data demonstrate that in a murine model of long-term common bile-duct ligation, survival and PTH are improved by pan-caspase inhibitor therapy. Circulating MP may have function by involving the PTH reduction mechanism(s) through target cell activation, however further investigation is needed. Emricasan is a promising agent for the treatment of PTH.

DISCLOSURES /FUNDINGS

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