Circulating microparticles carry apoptosis markers CK-18 and Caspase-3/7 which are reduced by treatment with emricasan in subjects with cirrhosis.

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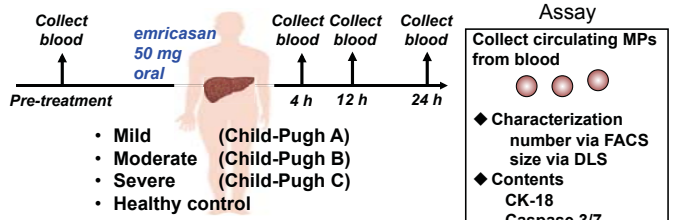
PURPOSE / AIM

★ During the progression of chronic liver diseases (CLDs), caspases promote apoptosis, leading dying cells to release apoptotic bodies and, as recently shown, microparticles (MPs) .

★ Caspase-dependent cell-derived MPs carry a variety of bioactive molecules that play a central role in liver inflammation and fibrosis. The pan-caspase inhibitor emricasan showed good efficacy and safety in reducing liver injury associated with cell death.

★ We AIM to investigate a direct effect of emricasan on damage-associated MP signals in subjects with mild, moderate and severe hepatic impairment.

METHODS



reference to the clinical study:
Spada, A. et. al. Rapid and statistically significant reduction of markers of apoptosis and cell death in subjects with mild, moderate and severe hepatic impairment with a single dose of the pan caspase inhibitor, emricasan. Hepatology 2014; 60: 1277A.

RESULTS

Circulating MP number pre-treatment

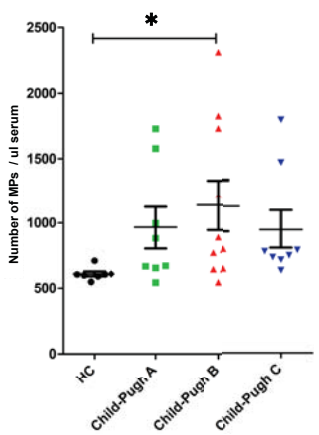


Figure 1. Circulating MP number via flow cytometry: Circulating MPs in pre-treatment were quantified using calcein positive MPs. The level of MPs were greater in Child-Pugh A and B compared to HC, with a statistically significant difference between HC and Child-Pugh B ($p<0.05$). [* $p<0.05$]

Circulating MP size with emricasan treatment

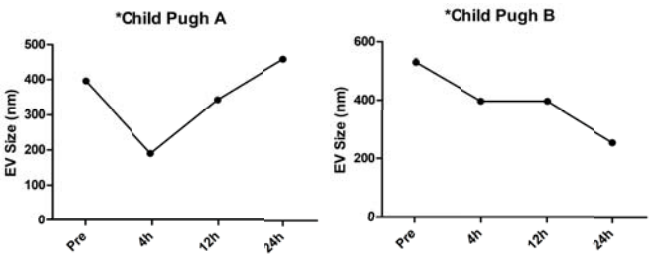
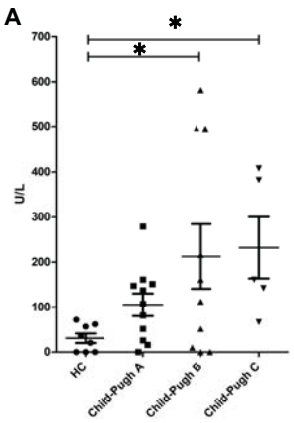
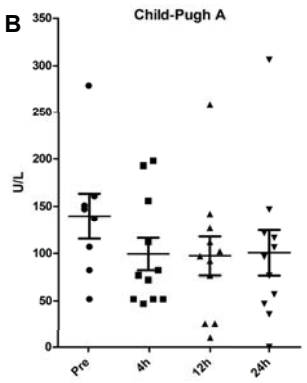


Figure 2. Circulating MP size via dynamic light scatter: Treatment with emricasan did not affect the total number of circulating MPs but resulted in a reduction in MP size particularly in Child-Pugh A and B.

CK-18 levels in MPs





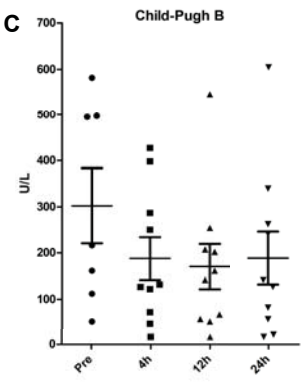
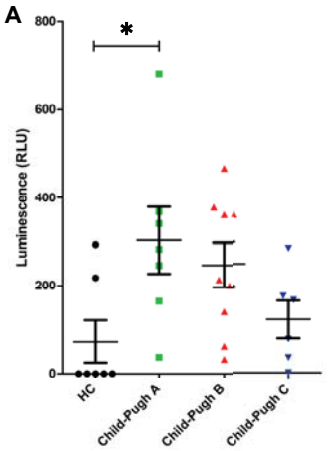
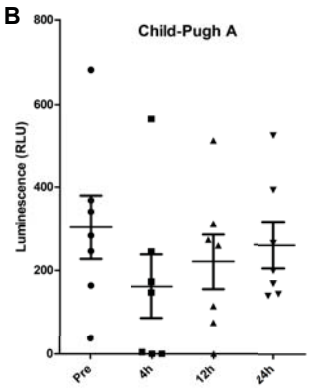


Figure 3. CK-18 levels in MPs (A) pre-treatment and (B,C) with emricasan treatment: (A) At baseline, MP-encapsulated titers of full-length and fragment CK-18 were elevated in subjects with advanced liver disease and increased along with the progression of the disease stage ($p<0.05$). **(B,C)** Treatment with emricasan reduced MP-encapsulated CK-18 levels with a maximal response observed after 4h post-treatment in **(B)** Child-Pugh A and **(C)** 12h in Child-Pugh B subjects. [* $p<0.05$]

Caspase-3/7 levels in MPs





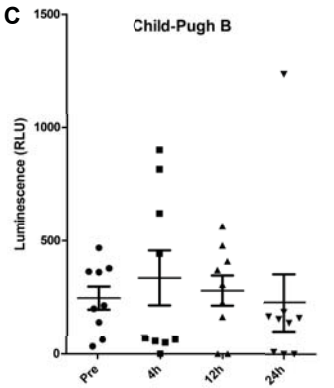


Figure 4. Caspase-3/7 levels in MPs (A) pre-treatment and (B,C) with emricasan treatment: (A) baseline levels of Caspase-3/7 were significantly elevated in MPs isolated from Child-Pugh A subjects compared to HCs ($p<0.05$) but not statistically different in Child-Pugh B and C groups. **(B,C)** Caspase-3/7 levels were reduced in Child-Pugh subjects particularly after 4h post-treatment of emricasan. [* $p<0.05$]

CONCLUSIONS

This study shows that subjects with severe hepatic injury have elevated levels of MPs in the bloodstream and that MPs carry CK-18 and caspase 3/7. Additionally, treatment with pan-caspase inhibitor emricasan, reduced to some extent the level of MP-encapsulated CK-18 and Caspase 3/7.

DISCLOSURES /FUNDINGS

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