angiogenic factors interacting with endothelium-specific receptor tyrosine kinase (Tie2) on endothelial cells (ECs), but their role in vascular remodeling during liver fibrosis is unknown. [Purpose] The purpose of this study is to elucidate the role of HSCs and angiopoietins on angiogenesis during liver fibrosis. [Methods] Liver fibrosis was induced in BALB/c mice by bile duct ligation (BDL) or by injection of carbon tetrachloride (CCl4) twice a week. Vessel density around the portal triads was determined by CD31 immunohistochemistry. Expression of angiopoietins was measured by quantitative real-time PCR in whole liver and isolated cell fractions. A human HSC cell line immortalized by expression of human telomerase reverse transcriptase (hTERT-HSC) was utilized to evaluate transcriptional regulation of angiopoietin-1 expression. Ad sTie2, an adenovirus expressing a soluble form of Tie2, was used to block angiopoietin signaling in mice in vivo. [Results] CD31 positive area was increased around the portal triads in fibrotic livers induced by BDL (0.26% to 0.60% at 2 weeks) or by CCl4 (0.26% to 0.62% at 2 weeks). Messenger RNA expression of angiopoietin-1 was upregulated after both BDL (2.8 fold) and CCl4 (3.1 fold). Kupffer cells, ECs, and HSCs express 5, 26, and 379 times as much angiopoietin-1 mRNA as hepatocytes, respectively, indicating HSCs are the main source of angiopoietin-1 in the liver. TNF-α (10 ng/ml) induced a 10-fold increase in angiopoietin-1 mRNA expression in hTERT-HSCs, and the induction was blocked by a proteosome inhibitor MG-132, an I-κB kinase inhibitor PS-1145, or an adenovirus expressing the I-κB superrepressor, indicating induction of angiopoietin-1 expression is NF-κB dependent. The soluble form of Tie2 was detectable in the mouse serum through 10 days after Ad sTie2 injection. Blockade of angiopoietin signaling in mice by Ad sTie2 injection prior to induction of liver fibrosis inhibited the increase in vessel density (0.44% vs 0.57% CD31-positive area) and the development of liver fibrosis (0.47% vs 1.13% sirius red-positive area) at 2 weeks after CCl4. [Conclusion] HSCs produce an angiogenic cytokine angiopoietin-1 that contributes to the development of liver fibrosis through promotion of angiogenesis. Ant-angiogenic drugs may be effective in treating hepatic fibrosis.

Disclosures:

The following people have nothing to disclose: KOJIRO TAURA, David A. Brenner

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INTERIM RESULTS OF RANDOMIZED CONTROLLED TRIAL OF ELAD™ IN ACUTE ON CHRONIC LIVER DISEASE

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This report details the first use of ELAD™ (Vital Therapies Inc, San Diego Ca, a human hepatocyte based liver assist device, in patients with acute on chronic liver disease. Methods: A randomized (2:1), open label, controlled trial of 90 patients was initiated at 2 Chinese liver disease centers. Continuous ELAD therapy was provided until recovery (43-119 hrs). Inclusion criteria were Chronic HBV or HCV with a current episode of acute decompensation. The primary endpoint was survival. 60 patients have currently been enrolled. 6 patients were not evaluable secondary to protocol violations leaving 35 treated and 19 controls to evaluate. All patients underwent one treatment of plasma exchange after randomization and obtaining baseline biochemical values. Demographic, and biochemical data is shown in the table. Results: 30 day transplant free survival was 9/19 (47%) in the controls and 30/35 (86%) in the treated group (p= 0.004). 5 patients underwent transplantation in the control group vs. 2 in the treated group. Intent to treat analysis: transplant free survival 10/20 (50%) controls vs.32/40 treated (80%) (p=0.034). Biochemical improvement supported the increased survival in the treated group. Safety endpoints: Thrombocytopenia was the only statistically significant safety issue. Platelets dropped by an average of 28% (see table) during ELAD therapy vs. no change in controls. Platelet count recovered within 5 days of ELAD discontinuation and could be managed by platelet transfusion. Conclusions: The first clinical trial of ELAD in acute on chronic liver disease patients was able to demonstrate that ELAD is safe in this patient population. There is statistically significant transplant free survival advantage for the ELAD treated patients. ELAD appears to be effective in bridging patients with acute decompensation of chronic liver disease to recovery.

	ELAD	CONTROL
AGE	39.6 ± 9.9	39.6 ± 11.6
HEP B	20/30 (67%)	13/16 (81%)
ON HBV ANTI-VIRAL @ BASELINE (%)	17	33
ON HBV ANTI-VIRAL @ POST ELAD DAY 7 (%)	25	42
ON HBV ANTI-VIRAL @ POST ELAD DAY 30 (%)	25	33
DURATION OF ELAD (HRS)	72 ± 14	
MELD @ BASELINE	28.4 ± 3.4	31.0 ± 5.7
MELD @ ELAD STOP	29.1 ± 6.6	30.1 ± 5.8
MELD @ POST ELAD DAY 6**	14.2 ± 5.3	16.0 ± 7.1
PLTS @ SCREEN	102.3 ± 38.8	100.8 ± 48.5
PLTS @ ELAD STOP***	51.7 ± 24.9	95.7 ± 66.7
PLTS @ POST ELAD DAY 6	94.9 ± 50.0	118.3 ± 52.9

* VALUE TAKEN AT 72 HRS (MEAN DURATION OF ELAD TREATMENT

**p <0.001 vs MELD at baseline and ELAD Stop

** P < 0.002

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John D. Brotherton - Employee: Other

Kameron Maxwell - Employee: Other

Michael Millis - Consultant/Adviser: Other

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OLDER AGE IS NOT ASSOCIATED WITH WORSE OUTCOMES IN ACUTE LIVER FAILURE

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Background: Age > 40 years is among the poor prognostic factors in King's College Hospital criteria for acute liver failure (ALF). Older age is considered a relative contraindication for liver transplantation in ALF. We aimed to evaluate the impact of older age, defined as age ≥ 60 years, on outcomes in patients with ALF. Methods: One thousand one hundred and twenty-six