Role of Immunomodulation Therapy with Selective Cytopheretic Device (SCD) in Reversing Acute on Chronic Liver Failure with Hepatorenal Syndrome and Multi-Organ Failure

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Introduction

Alcohol associated liver disease (ALD) is on the rise and has become the leading indication for liver transplantation in United States. Acute on chronic liver failure (ACLF) is a clinical disorder characterized by acute clinical deterioration in patients with pre-existing chronic liver disease. ACLF appears to develop from systemic inflammation, often due to bacterial infections or alcoholic hepatitis, and progresses to multi-organ failure. Severe ACLF with ≥ 4 organ failure has a grave prognosis with a mortality rate at 28 days of 100%. Early liver transplant is the treatment of choice for those who are refractory to medical treatment. Intervention to modulate and lessen this systemic inflammatory state may alter the progression of multi-organ dysfunction and allow time for liver transplantation.

Methods and Materials

A male patient in his early 30s presented with acute alcohol associated hepatitis, acute on chronic liver failure, profound hepatic encephalopathy and hepatorenal syndrome. He had greater than four organ failures requiring vasopressors, mechanical ventilation, and continuous renal replacement therapy. He was enrolled into a clinical trial (NCT 04898010) to evaluate an extracorporeal immunomodulating device, SCD.

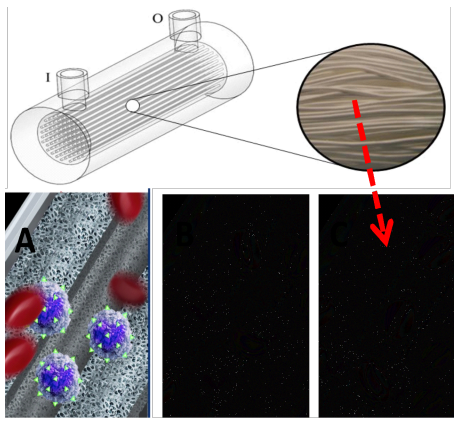

Figure 1. SCD Design Schematic and Mechanism of Action Diagram. SCD consists of a polycarbonate housing with an inlet (I) and outlet (O) for blood, and potted polysulfone based fibers. Circular blow-up of the fibers are shown, with dashed red arrow pointing to Panel C, showing release of the immuno-modulated leukocyte (LE). Panel A: binding (catch) of activated LE. Panel B: "reset" LE. Erythrocytes are red, LE are purple and LE binding sites, acutely mobilized to the surface of activated LE are green (Panel A).

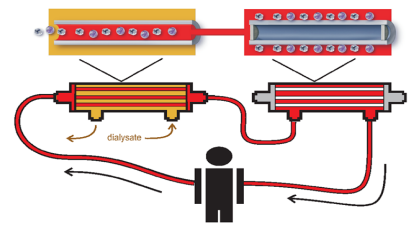

Figure 2. SCD Device Schematic

Results

Treatment with this device resulted in rapid improvement with discontinuation of vasopressors on day 2, extubation on day 4 and transitioned to intermittent hemodialysis on day 7. This treatment was associated with a decline in elevated blood cytokine concentrations and diminution of activation levels of circulating leukocytes (Table, Figure 3 and Figure 4). On follow up he was alive on day 90 post treatment and being evaluated for liver transplantation.

Clinical and laboratory values

	Admission	Day 0	Day 2	Day 4	Day 6	End	120 hours Post-SCD	Follow-up Day 30	Follow-up Day 90
Absolute Complete Blood Counts									
WBC (10^3/mL)	15.4	20.8	15.9	32.1	35.4	29.9	23.9	23.3	22.6
Neutrophil (10^3/mL))	12.5	18.0	12.1	23	26.8	22.2	20.2	16.7	15.1
Monocyte (cells/mL)	1400	400	1100	4400	4100	3600	2600	2500	4300
Platelet count (10^3/mL)	177	106	45	47	71	93	171	318	234
Liver Function tests									
AST (units/L)	207	316	180	168	161	158	153	148	77
ALT (units/L)	114	115	112	114	38	24	11	105	62
Alkaline Phosphatase (units/L)	112	88	119	146	135	112	105	108	98
Bilirubin (mg/dL)	29.8	30.1	28.6	24.7	22.2	19.7	23.5	18.1	19.2
Albumin (g/dL)	1.9	2.3	2.4	2.4	2.2	2	2.2	1.7	1.7
INR	2.7	1.6	1.6	1.4	1.4	1.5	1.6	1.7	1.8
Immunologic Markers (pg/mL)									
IL-6 (normal 0-16)	NA	210	26	19	40	30	40	NA	NA
IL-8 (normal 24-39)	NA	300	152	91	121	67	121	NA	NA
IL-10 (normal 8-16)	NA	3.8	<1	<1	<1	<1	<1	NA	NA
IL-1RA (normal 178-558)	NA	12738	3815	2109	2984	1299	39	NA	NA
MCP-1 (normal 20-80)	NA	48	22	26	33	43	50	NA	NA

NA, Not Available; IL., Interleukin; RA, Receptor Antagonist; MCP, Monocyte Chemoattractant Protein
a. These samples were obtained immediately before CRRT-SCD initiation

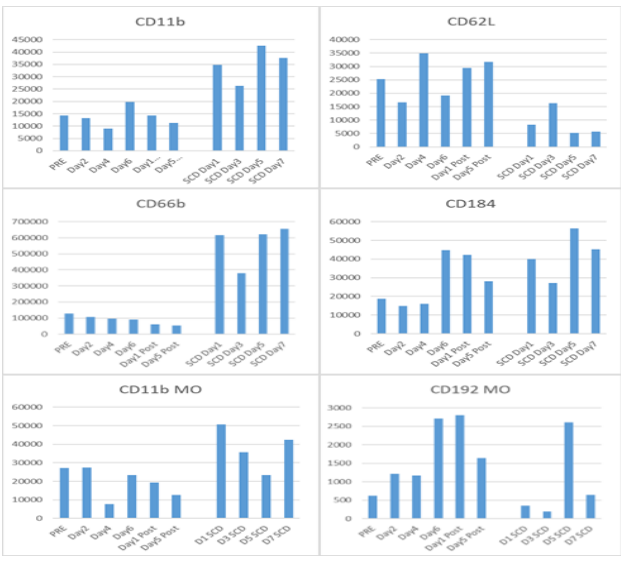

Figure 3. Selective cytopheretic device (SCD) treatment effects on leukocytes by cytometric analysis. Each graph displays the MFI of various cell surface markers on either circulating blood neutrophils (top 4 panels) or monocytes (bottom 2 panels) during the 7 day course of daily SCD treatment. Also displayed are the MFIs of the eluted neutrophils or monocytes from the SCD after treatments on days 1, 3, 5, and 7. All monocyte graphs depict the MFI of the entire monocyte population

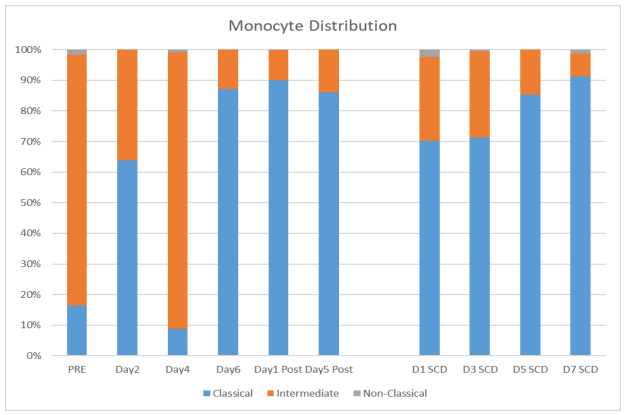

Figure 4. Percent distribution of various subsets of circulating monocytes prior to, during and after 7 days of SCD treatment. Classical (CD14++CD16-), intermediate (CD14+CD16+), non-classical (CD14+CD16++) are displayed. Also depicted are the percent distribution of these subsets in the eluted monocyte pool from the SCD after treatments on days 1, 3, 5, and 7.

Discussion

As shown in Table, improvements in organ dysfunctions in this patient was chronologically associated with reductions in multiple inflammatory biomarkers, including IL-6, IL-8, IL-10, IL-1RA, and MCP-1. This reduction in systemic cytokines were related to substantive changes in the circulating phenotype of neutrophils and monocytes.

As shown in Figure 3, SCD binds the more pro-inflammatory neutrophils and monocytes (CD11b) compared to circulating blood. Upon binding to the SCD membrane, neutrophils release L-selectin (CD62L) as seen as a reduction of MFI for CD62L from blood to eluded (bound) neutrophils. Upon binding, neutrophils degranulate as demonstrated as a rise in CD66b MFI in bound cells compared to circulating blood. In addition, bound neutrophils are promoted in the low ionized calcium environment of the SCD into apoptosis, as reflected in the increase of CD184 (CXCR4 receptor for stromal derived factor-1/CXCL12) MFI on bound neutrophils and the rise in circulating blood neutrophils MFI. The CXCR4/CXCL12 chemokine axis is critical in the trafficking of senescent/apoptotic neutrophils for clearance from blood. The increase in circulating monocyte CD192 (CXR2 receptor for monocyte chemoattractant protein-1/CCL2) may reflect a decline in circulating levels of MCP-1, a critical factor for monocyte migration into damaged tissue, during SCD therapy.

As shown in Figure 4, a dramatic increase in circulating pro-inflammatory intermediate monocytes (CD14+CD16+) were present before SCD therapy (intermediate monocytes are usually 5-10% of circulating pool in normal individuals). This pro-inflammatory pool was significantly reduced after initiation of SCD treatment declining from 82 to 36% of the circulating pool. But on day 4 a rebound of this subtype was seen increasing from 36 to 90%. This increase was most likely due to release from a sequestered splenic pool of monocytes, as has been seen in disease states of chronic inflammation. By day 6 the normal balance of classical (CD14+CD16-)/intermediate subsets was restored and persisted during the post treatment period.

Conclusions

Improvements in organ dysfunctions in this patient was chronologically associated with reductions in multiple inflammatory biomarkers, including IL-6, IL-8, IL-10, IL-1RA, and MCP-1. This reduction in systemic cytokines were related to substantive changes in the circulating phenotype of neutrophils and monocytes. This approach may be an effective therapy to bridge patients with ACLF and AKI/HRS to liver transplantation.