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IMPACT OF THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME ON 3-MONTH MORTALITY RATES IN SUBJECTS WITH SEVERE ALCOHOLIC HEPATITIS TREATED WITH THE ELAD® SYSTEM

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BACKGROUND

Systemic Inflammatory Response Syndrome (SIRS) is a major predictor of multi-organ failure (MOF) and mortality in subjects with severe alcoholic hepatitis (sAH). [1] Criteria for definition of SIRS are listed in Table 1[2].

Table 1. Criteria for Diagnosis of SIRS

Two or more of the following	
White blood cell count	>12 or <4 x 10^3/mL
Pulse	>90 beats/min
Temperature	>38°C or <36°C
Respiratory rate	>20 breaths/min

STUDY OBJECTIVE

Our aim was to determine whether the presence of SIRS had an impact on the mortality rate in ELAD treated versus Control sAH subjects when stratified by MELD <28 vs MELD ≥28.

MATERIALS & METHODS

A randomized, open-label, multicenter, controlled study was conducted in subjects ≥18yrs old with a clinical or histologic diagnosis of sAH, bilirubin ≥8mg/dL, Maddrey discriminant function (DF) score ≥32, MELD score of 18-35 and platelets ≥40,000/mm3, without severe concomitant disease, uncontrolled sepsis or bleeding, hemodynamic instability or need for chronic dialysis. Subjects were randomized to either protocol-specified standard of care (SOC, Control group) or SOC plus 3-5 days continuous treatment with an investigational extracorporeal human allogeneic cellular liver system (ELAD) consisting of human C3A hepatoblastoma cells contained in four cartridges (ELAD group). SOC was based on AASLD and EASL guidelines.

RESULTS

203 subjects were randomized (ELAD 96, Control 107). Using intent-to-treat analysis, the overall and 91d survival rates were similar in the two groups. Pre-specified subgroups of baseline MELD <28 (n=120) and age <median (n=101) reported trends towards improved survival in the ELAD group. Of the 203 subjects, 122 had a white blood cell count >12 or <4 x 103/mL, 93 had a pulse >90 beats/min, 13 had a temperature >38°C or <36°C, and 22 had a respiratory rate >20 breaths/min. In the ELAD group, 36/96 (37.5%) subjects compared with 31/107 (29.0%) subjects in the Control group had 2 or more of these criteria and had SIRS at randomization. Of these subjects who had SIRS at randomization, 14 and 13 subjects were receiving steroids in the ELAD and Control groups, respectively) (Table 2). There was no difference of 91-d survival between subjects with or without SIRS at baseline (Table 3). In subjects with SIRS and MELD <28, the 3-month mortality rate in the ELAD group was 3/20, 15% compared with 7/17, 41% in the Control group (p=0.07). However, in subjects with SIRS and MELD ≥28, the 3-month mortality rate in the ELAD group was 12/16, 75% compared with 5/14, 36% in the Control group (p=0.03) (Table 4).

Table 2. SIRS by Treatment Group at Baseline

	ELAD (n=96)	Control (n=107)	Total (n=203)
Number of Subjects with SIRS at Baseline			
Presence of SIRS (meet at least 2 criteria)	36	31	67
SIRS Parameters			
White blood cell count >12 or <4 x 10^3/mL and Pulse >90 beats/min	31*	25**	56
White blood cell count >12 or <4 x 10^3/mL and Temperature >38°C or <36°C	2	0	2
White blood cell count >12 or <4 x 10^3/mL and Respiratory rate >20 breaths/min	2	3	5
Pulse >90 beats/min and Respiratory rate >20 breaths/min	1	2	3
Pulse >90 beats/min and Temperature >38°C or <36°C	0	1	1
Taking corticosteroids	14/36 (39%)	13/31 (42%)	27/67 (40%)

*Among these 31 subjects, 3 subjects also had temperature <36°C; 5 subjects also had respiratory rate>20 breaths/min

**Among these 25 subjects, 4 subjects also had respiratory rate>20 breaths/min; 2 subjects also had Temperature >38°C or <36°C and 2 subjects met all four SIRS criteria

Table 3. 91-d Survival by SIRS by Treatment Group

SIRS-Yes	Total	Deaths	Mortality
ELAD	36	15	15/36 (42%)
Control	31	12	12/31 (39%)
SIRS-No	Total	Deaths	Mortality
ELAD	60	24	24/60 (40%)
Control	76	29	29/76 (38%)

Table 4. 91-d Outcome of Subjects by SIRS at Baseline by Treatment Group by MELD

MELD<28	Total	Alive	Dead	Lost to Follow-up	Mortality	Chi-square p-value
ELAD	20	16	3	1	3/20 (15%)	0.07
Control	17	9	7	1	7/17 (41%)	
MELD≥28	Total	Alive	Dead	Lost to Follow-up	Mortality	Chi-square p-value
ELAD	16	4	12	0	12/16 (75%)	0.03
Control	14	9	5	0	5/14 (36%)	

CONCLUSIONS

In sAH subjects with SIRS and MELD <28, lower 3-month mortality rates were observed when treated with ELAD plus SOC compared to SOC alone. However, in subjects with SIRS and MELD ≥28, 3-month mortality rates were higher in the ELAD group when compared to SOC. A current prospective randomized controlled clinical study in subjects with sAH and MELD <30, including subjects with SIRS, is underway.

REFERENCES

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