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BOTH MELD SCORE AND NUMBER OF ORGAN FAILURES DEFINED BY THE LATEST CHRONIC LIVER FAILURE-ORGAN FAILURE SCORING SYSTEM EFFECTIVELY SELECT SUBJECTS WITH SEVERE ALCOHOLIC HEPATITIS WITH GOOD OUTCOMES WHEN TREATED WITH THE ELAD® SYSTEM

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BACKGROUND

Mortality due to severe alcoholic hepatitis (sAH) is related to organ failures (OF)[1] (Table 1), MELD score, presence of Systemic Inflammatory Response Syndrome (SIRS), and concurrent infections at presentation that impact the prognosis and response to medical treatment.

Table 1. Chronic Liver Failure-Organ Failure Score system

Organ/system	Subscore = 1	Subscore = 2	Subscore = 3
Liver OR vs. subscore 1 (95% CI)	Bilirubin < 6 mg/dL	6 ≤ Bilirubin ≤ 12 mg/dL OR = 2.6 (1.6–4.3)	Bilirubin >12 mg/dL OR = 7.1 (4.7–10.7)
Kidney OR vs. subscore 1 (95% CI)	Creatinine < 2 mg/dL	2 ≤ Creatinine < 3.5 mg/dL OR = 3.8 (2.3–6.3)	Creatinine ≥ 3.5 mg/dL or renal replacement OR = 15.5 (8.9–26.8)
Brain (West Haven grade for HE) OR vs. subscore 1 (95% CI)	Grade 0	Grades 1–2 OR = 2.1 (1.4–3.2)	Grades 3–4[a] OR = 9.7 (5.9–16.1)
Coagulation OR vs. subscore 1 (95% CI)	INR < 2.0	2.0 ≤ INR < 2.5 OR = 5.2 (3.4–7.9)	INR ≥ 2.5 OR = 7.5 (4.6–12.3)
Circulatory OR vs. subscore 1 (95% CI)	MAP ≥ 70 mm Hg	MAP < 70 mm Hg OR = 2.3 (1.6–4.3)	Use of vasopressors OR = 9.2 (5.2–16.4)
Respiratory PaO_2/FiO_2 or SpO_2/FiO_2 OR vs. subscore 1 (95% CI)	> 300 > 357	≤ 300–> 200 > 214–≤ 357 OR = 2.7 (1.7–4.2)	≤ 200[b] ≤ 214[b] OR = 6.4 (3.1–13.2)

Abbreviations: FIO_2, fraction of inspired oxygen; HE, hepatic encephalopathy; INR, international normalized ratio; MAP, mean arterial pressure; OR, odds ratio; 95% CI, 95% confidence interval; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation.
Note: The shaded area denotes criteria for diagnosing organ failures.
[a]Patients submitted to mechanical ventilation due to HE and not to a respiratory failure were considered as presenting a cerebral failure (cerebral subscore = 3).
[b]Other patients enrolled in the study with mechanical ventilation were considered as presenting a respiratory failure (respiratory subscore = 3).

STUDY OBJECTIVE

Our aim was to determine whether MELD and CLIF-SOFA organ failure could be used to predict the prognosis and response to ELAD treatment in sAH subjects in a Phase 3 study.

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/mm^3, without severe concomitant disease, uncontrolled sepsis or bleeding, hemodynamic instability or need for chronic dialysis. Subjects were randomized 1:1 to receive protocol-specified standard of care (SOC) based on AASLD and EASL guidelines alone (Control) or SOC with 3-5 days of continuous treatment with the ELAD system consisting of human C3A hepatoblastoma cells contained in four cartridges (ELAD).

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. The prevalence and number of organ failures in the patients at baseline are summarized in Table 2. 76/203 subjects (32 ELAD; 44 Control) had two or more OF (liver, kidney, brain, coagulation, circulatory and/or respiratory) at baseline, based on criteria defined in the Chronic Liver Failure-OF (CLIF-OF) score system for acute-on-chronic liver failure (ACLF)[1]. 191/203 (94%) had at least one OF, of which one OF was due to liver failure. Six subjects had only one OF in other body systems (1 Brain, 4 Coagulation and 1 Circulatory) and six other subjects (ELAD 2, Control 4) did not have any OFs (Table 3). Of subjects with 2 or more OFs, more ELAD than Control subjects died by d91 (20/32, 63% vs 19/44, 43%, respectively; p=N.S.). In subjects with only one OF (ELAD 62/96, 65% vs Control 59/107, 55%), fewer ELAD (19/62, 31%) than Control subjects (21/59, 36%) died by d91 (p=N.S.). Only one Control of six subjects with no OFs died by d91 (Table 4). 135/203 subjects (ELAD 61, Control 74) had baseline MELD ≤28. In subjects with baseline MELD≤28, fewer ELAD (14/61, 23%) than Control subjects (27/74, 36%) died by d91 (p=0.09). 68/203 subjects (ELAD 35, Control 33) had MELD ≥28 at baseline and in this group, more ELAD (71%) than Control subjects (42%) died by d91 (p<0.05) (Table 5).

Table 2. Prevalence and Number of Organ Failures at Baseline

	Patients (n=203)	Prevalence (%)
Number of organ failures at baseline		
No organ failure	6	0.03
1 organ failure	121	0.60
2 or more organ failures	76	0.37
Type of organ failure at baseline		
Liver failure	191	0.94
Renal failure	9	0.04
Coagulation failure	41	0.20
Cerebral failure	12	0.06
Circulatory failure	38	0.19
Respiratory failure	2	0.01

Table 3. Prevalence and Number of Organ Failures by Treatment Group at Baseline

Overall	≥2 Organ failures	1 Organ failure	No organ failure
ELAD (n=96)	32/96 (33%)	62/96 (65%)	2/96 (2%)
Control (n=107)	44/107 (41%)	59/107 (55%)	4/107 (4%)

Table 4. 91-d Outcome by Treatment Group by Number of Organ Failure

≥2 Organ failures	Total	91-d mortality rate
ELAD	32	20/32 (63%)
Control	44	19/44 (43%)
1 Organ failure	Total	91-d mortality rate
ELAD	62	19/62 (31%)
Control	59	21/59 (36%)
0 Organ failure	Total	91-d mortality rate
ELAD	2	0
Control	4	1/4 (25%)

Table 5. 91-d Outcome by Treatment Group by MELD (≤28 vs. >28)

MELD≤28	Total	Death	91-d mortality rate
ELAD	61	14	14/61 (23%)
Control	74	27	19/44 (36%)
p value		0.09	
MELD>28	Total	Death	91-d mortality rate
ELAD	35	25	25/35 (71%)
Control	33	14	14/33 (42%)
p value		<0.05	

CONCLUSIONS

Both MELD ≤28 and restricting subjects to only liver failure are effective at predicting subjects who are likely to have a favorable response to treatment with ELAD. A new study is now enrolling that excludes subjects with evidence of secondary organ failures to avoid enrollees likely to have an unfavorable response to treatment with ELAD.

REFERENCES

[1]Arroyo V, Jalan R. Acute-on-chronic liver failure: definition, diagnosis, and clinical characteristics. InSeminars in liver disease 2016 May (Vol. 36, No. 02, pp. 109-116). Thieme Medical Publishers.

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