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PHOSPHATIDYLETHANOL (PEth) IN BLOOD AS MARKER OF ALCOHOL RELAPSE (AR) IN SUBJECTS WITH SEVERE ALCOHOLIC HEPATITIS (sAH) IN THE ELAD PHASE 3 CLINICAL TRIAL

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BACKGROUND

Severe Alcoholic Hepatitis (sAH) is associated with high mortality. No therapy has improved short- or long-term mortality and alcohol relapse (AR) may adversely affect clinical outcome. Self-reporting of AR is unreliable and likely underestimates alcohol consumption. PEth is an abnormal phospholipid formed through the transphosphatidylation action of the enzyme phospholipase D when ethanol is present.[1] The blood PEth test has been evaluated as a promising alcohol consumption biomarker in a number of study populations.[2, 3] A positive (>20ng/mL) PEth blood test result is reported to have 73% sensitivity for any alcohol drink over the previous 4 weeks and false positives have not been found.[2, 4]

OBJECTIVES

Our aim was to determine whether PEth could be used to establish AR and to examine the characteristics of AR in a Phase 3 study of the ELAD System.

METHODS

Adults with sAH were randomized 1:1 to standard of care (SOC) plus continuous 3-5d ELAD treatment (ELAD) or SOC alone (Control). Blood samples for PEth testing were obtained at randomization, hospital discharge, and then weekly thereafter during home visits until 91d post-randomization and analyzed by a central lab. Self-reporting of alcohol consumption was obtained weekly post-discharge using the timeline followback calendar. Primary outcome was survival at 91d. No data were revealed until after study data lock.

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. 120/203 subjects were discharged (56/96 ELAD, 64/107 Control). 91/120 (76%) of discharged subjects were still alive at 91d.

RESULTS (cont.)

AR by PEth, defined as at least one positive post-discharge PEth result, occurred in 49/120 (41%) of discharged subjects. 4/49 (8%) of these subjects had a negative PEth result at screen. Fewer ELAD-treated subjects had AR by PEth than Controls (16/56, 29% vs 33/64, 52%, p<0.05). 19 subjects self-reported AR. Of the 49 subjects with AR by PEth, only 14/49 (29%) self-reported AR (p<0.05, Table 1). Of the 19 subjects with self-reported AR, 14/19 (74%) had AR by PEth (Figure 1). 45/49 (92%) subjects with evidence of AR by PEth were alive at 91d vs 46/71 (65%) with no evidence of AR by PEth (p<0.05, Table 2). Subjects with AR by PEth were significantly younger, and had significantly lower MELD, creatinine and bilirubin level at screen and discharge than those without AR by PEth (p<0.05) (Table 3). Average PEth results were 427.1 ng/mL and 225.6 ng/mL, for ELAD and Control respectively (p=0.08). 12/16 (75%) ELAD subjects vs 17/33 (52%) Control subjects with AR by PEth (p=0.11) had more than 2 positive post-discharge PEth tests.

Table 1. Subject Disposition

	# of Randomized Subjects	# of Discharged Subjects	# of AR by PEth Subjects	# of Self-reported Alcohol Intake Subjects
ELAD	96	56/96 (58%)	16/56 (29%)	7/56 (13%)
Control	107	64/107 (60%)	33/64 (52%)	7/64 (11%)

Figure 1. PEth test vs. Self-reported Alcohol Intake

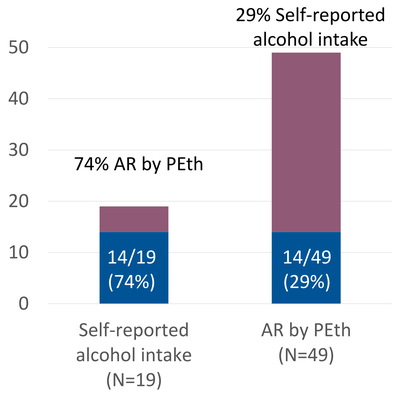

Table 2. Proportion of Survivors at 91d by Alcohol Relapse subgroups

	N	91d		Overall	
		Dead	Alive	Dead	Alive
AR by PEth-yes	49	4 (8%)	45 (92%)	9 (18%)	40 (82%)
AR by PEth-no	71	25 (35%)	46 (65%)	28 (39%)	43 (61%)
Chi-square p-value		<0.05		<0.05	

Table 3. Laboratory at Screen and Discharge

At Screen	N	Age	MELD	INR	Creatinine (mg/dL)	Bilirubin (mg/dL)
AR by PEth-yes	49	42.6	25.6	2	0.7	21.7
AR by PEth-no	71	47.9	27.7	1.9	1.3	26.3
T-test p-value		<0.05	<0.05	N.S.	<0.05	<0.05
At Discharge	**N**	**Missing data**	**MELD**	**INR**	**Creatinine (mg/dL)**	**Bilirubin (mg/dL)**
AR by PEth-yes	49	6/49	23.2	1.8	0.8	16
AR by PEth-no	71	14/71	27.6	2	1.4	20.6
T-test p-value			<0.05	N.S.	<0.05	<0.05

CONCLUSIONS

PEth testing could be applied routinely to determine post-discharge AR in a population of sAH subjects followed for 91d. Self-reporting significantly underestimated AR compared with PEth. Higher AR in Control subjects did not adversely affect 91d survival or confound interpretation of study outcome. PEth test data past 91d were not obtained so the impact of extended AR on survival could not be estimated from this study. AR was inversely related to sAH disease severity at screen and discharge. As healthier subjects were more prone to AR, it is not surprising that there were significantly fewer deaths in subjects with AR during the 91d follow up period. As fewer ELAD subjects had AR at 91d, it is possible that ELAD treatment discourages AR. PEth can play an important role in identifying those patients recovering from sAH who have AR, and who may be healthy enough for additional rehabilitation interventions.

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