Serum VEGF levels are associated with cognition and functioning in AD: Influence of the treatment with Cerebrolysin and donepezil

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BACKGROUND

Vascular endothelial growth factor (VEGF) is an angiogenic growth factor showing neuroprotective, neurotrophic and cognitive effects in experimental conditions that might be relevant for the treatment of Alzheimer's disease (AD) patients, but changes in circulating VEGF and the interactions of VEGF with clinical responses after drug treatment have not been investigated in AD

MATERIALS AND METHODS

Serum VEGF levels, cognitive and functional performance were evaluated in AD patients treated with Cerebrolysin (n=52), donepezil (n=52), or a combination of both drugs (n=53) in a 28-week double-blind, randomized clinical trial. VEGF levels were measured in serum samples by using specific ELISA kits for VEGF[165] in serum samples obtained at baseline, at week-16 (end of active Cerebrolysin treatment) and at week-28 (endpoint).

RESULTS

Overall, there were no significant treatment effects on VEGF levels (Table 1).

Table 1. Effects of Cerebrolysin, donepezil and combined therapy on VEGF serum levels in AD patients

	Cerebrolysin (n=52)	Donepezil (n=52)	Combined Therapy (n=53)	Analysis		
	Mean ± SD	Mean ± SD	Mean ± SD	X^2	df	p
Baseline VEGF (pg/ml)	310.79±284.11	372.23±249.35	357.97±303.36	3.52	2	0.172
Week-16 VEGF (pg/ml)	324.18±299.35	388.97±319.71	346.32±246.46	3.19	2	0.202
Week-28 VEGF (pg/ml)	327.92±364.15*	402.13±287.08	377.06±284.63	6.34	2	0.042
	N (%)	N (%)	N (%)	X^2	df	p
Female gender	38 (73.1)	40 (76.9)	43 (81.1)	0.96	2	0.617
APOE ε4 allele	24 (46.2)	24 (46.2)	21 (39.6)	0.608	2	0.738
CIBIS+				2.5	4	0.642
3	14 (26.9)	18 (34.6)	21 (39.6)			
4	22 (42.3)	20 (38.5)	16 (30.2)			
5	16 (30.8)	14 (26.9)	16 (30.2)			
	Mean ± SD	Mean ± SD	Mean ± SD	F	df	p
Age (years)	74.65±6.65	75.50±7.43	72.89±8.13	1.69	2, 154	0.187
Platelets (x10⁹/L)	229.00±68.01	223.79±43.76	223.13±57.72	0.16	2, 154	0.849
MMSE (score)	17.27±4.25	17.46±4.27	17.75±4.67	1.45	2, 154	0.238
Baseline ADAS-cog+	41.15±15.55	40.51±16.21	39.79±17.89	0.09	2, 154	0.915
Baseline ADCS-ADL	48.13±19.73	52.62±20.15	54.17±19.95	1.29	2, 154	0.278

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In moderately severe AD cases:

The combination therapy reduced elevated VEGF levels significantly (p<0.05) at week-16 and week-28 as compared to donepezil alone (Figure 1).

Higher baseline VEGF levels were associated to improvements in cognition (ADAS-cog+) and functioning (ADCS-ADL) (figure 2a,b,c)

VEGF reductions at week-28 correlated with improvements in ADAS-cog+ praxis & executive functions (Figure 2d).
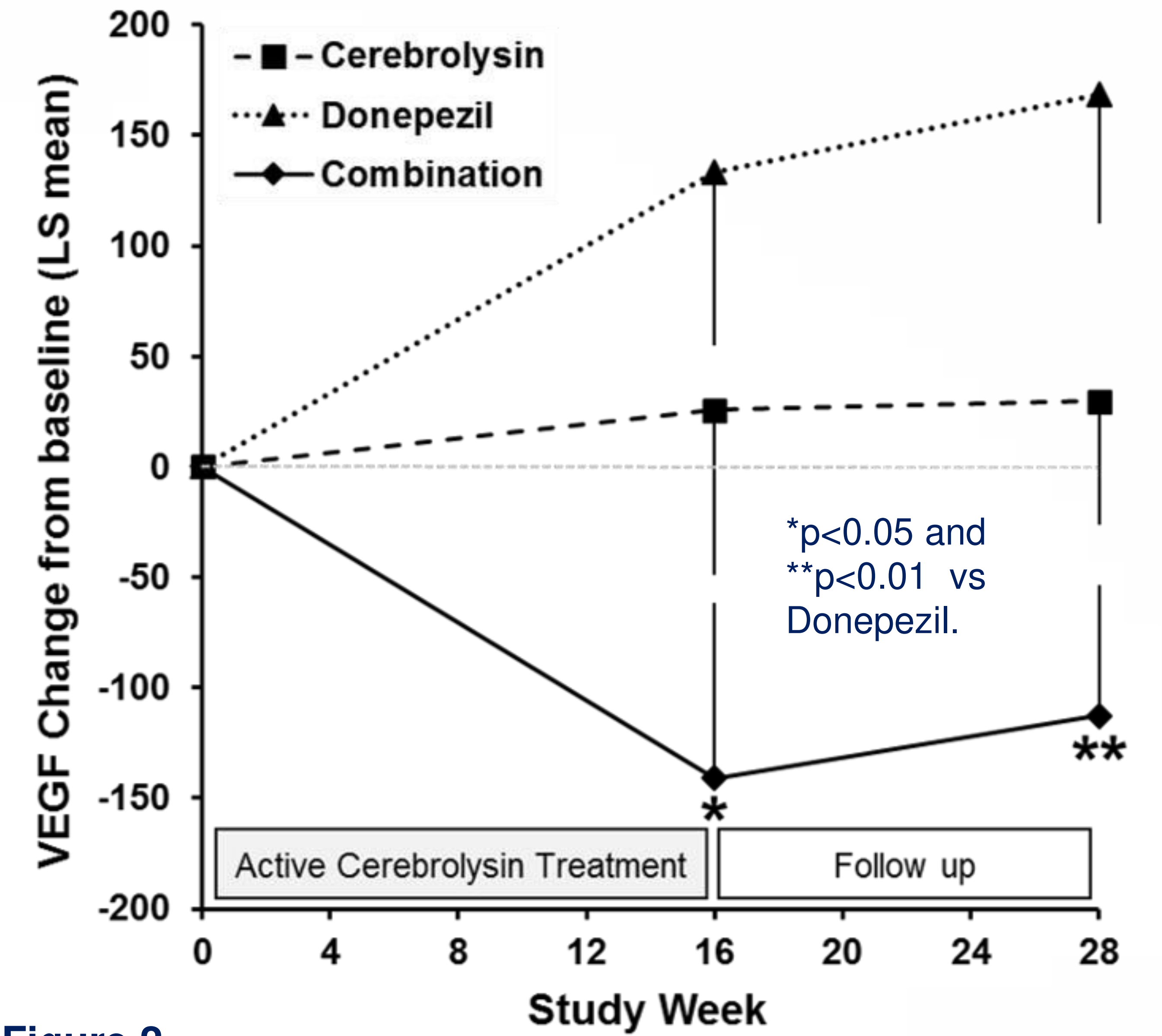
Figure 1.

*p<0.05 and **p<0.01 vs Donepezil.

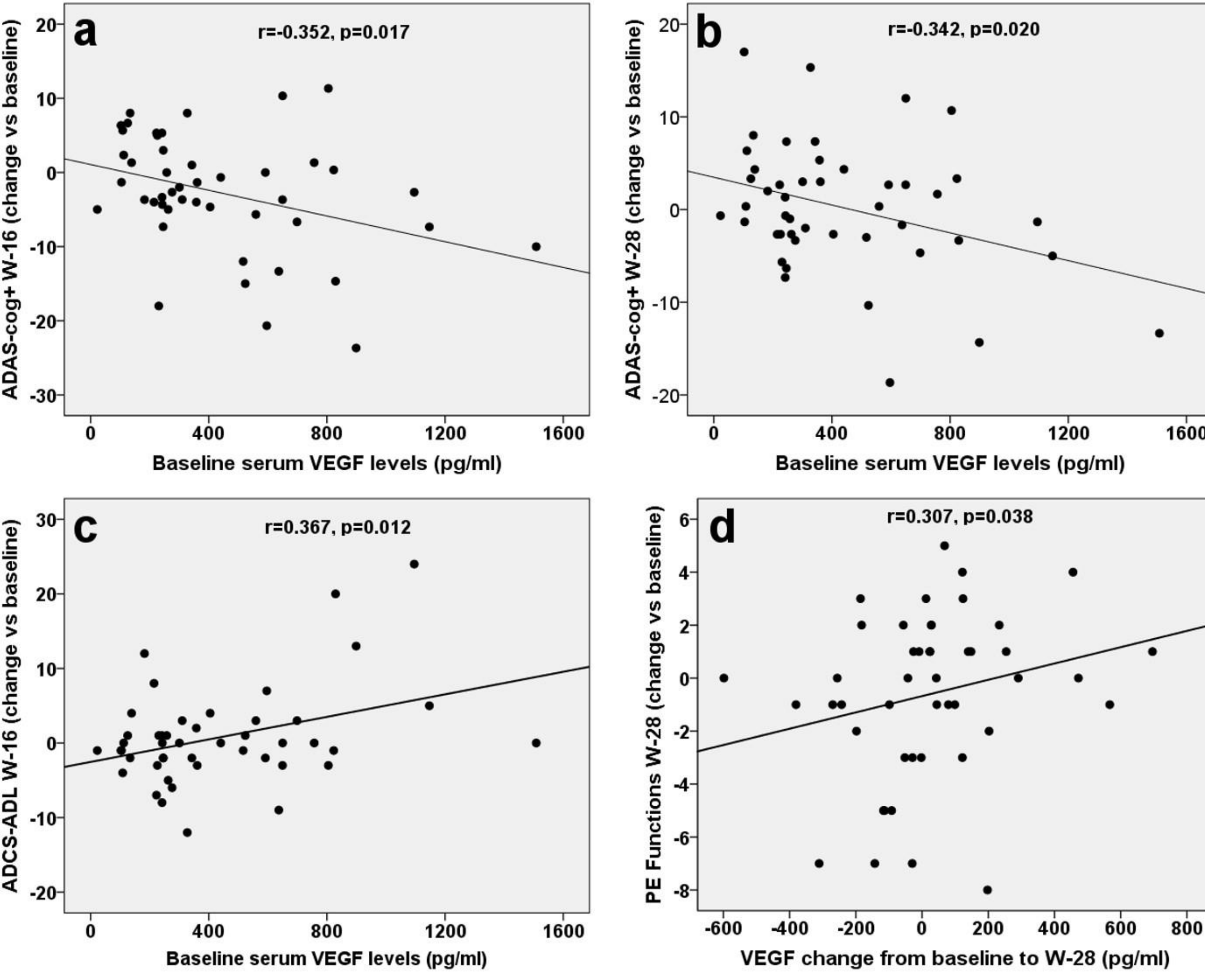Active Cerebrolysin Treatment | Follow up

Figure 2.

Table 2. VEGF levels and clinical characteristics in subgroups of AD patients stratified by VEGF changes from baseline to W-28 (reduction vs increase).

	VEGF Reduction Group (n=79)	VEGF Increase Group (n=78)	Analysis		
	Mean ± SD	Mean ± SD	X^2	df	p
Baseline VEGF (pg/ml)	386.37±289.18	307.26±265.11	4.44	1	0.035
Week-16 VEGF (pg/ml)	318.50±264.22	388.17±310.59	2.29	1	0.130
Week-28 VEGF (pg/ml)	281.80±245.77	457.49±349.46	14.15	1	0.000
	N (%)	N (%)	X^2	df	p
Female gender	58 (73.4)	63 (80.8)	1.20	1	0.273
APOE ε4 allele	30 (38.0)	39 (50.0)	2.30	1	0.129
CIBIS+			0.44	2	0.803
3	25 (31.6)	28 (35.9)			
4	31 (39.2)	27 (34.6)			
5	23 (29.1)	23 (29.5)			
	Mean ± SD	Mean ± SD	F	df	p
Age (years)	74.10±7.13	74.58±7.82	0.16	1, 155	0.691
Platelets (x10⁹/L)	229.06±63.31	221.47±50.05	0.20	1, 155	0.657
MMSE (score)	17.34±4.35	17.65±4.42	0.69	1, 155	0.406
Baseline ADAS-cog+ (score)	40.69±15.73	40.26±17.33	0.03	1, 155	0.871
Baseline ADCS-ADL (score)	51.68±18.88	51.63±21.16	0.00	1, 155	0.986

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Independently of treatment, AD patients with VEGF reductions compared to those with VEGF increases at week-28 showed better improvements in cognition and functioning at endpoint (Figure 3).
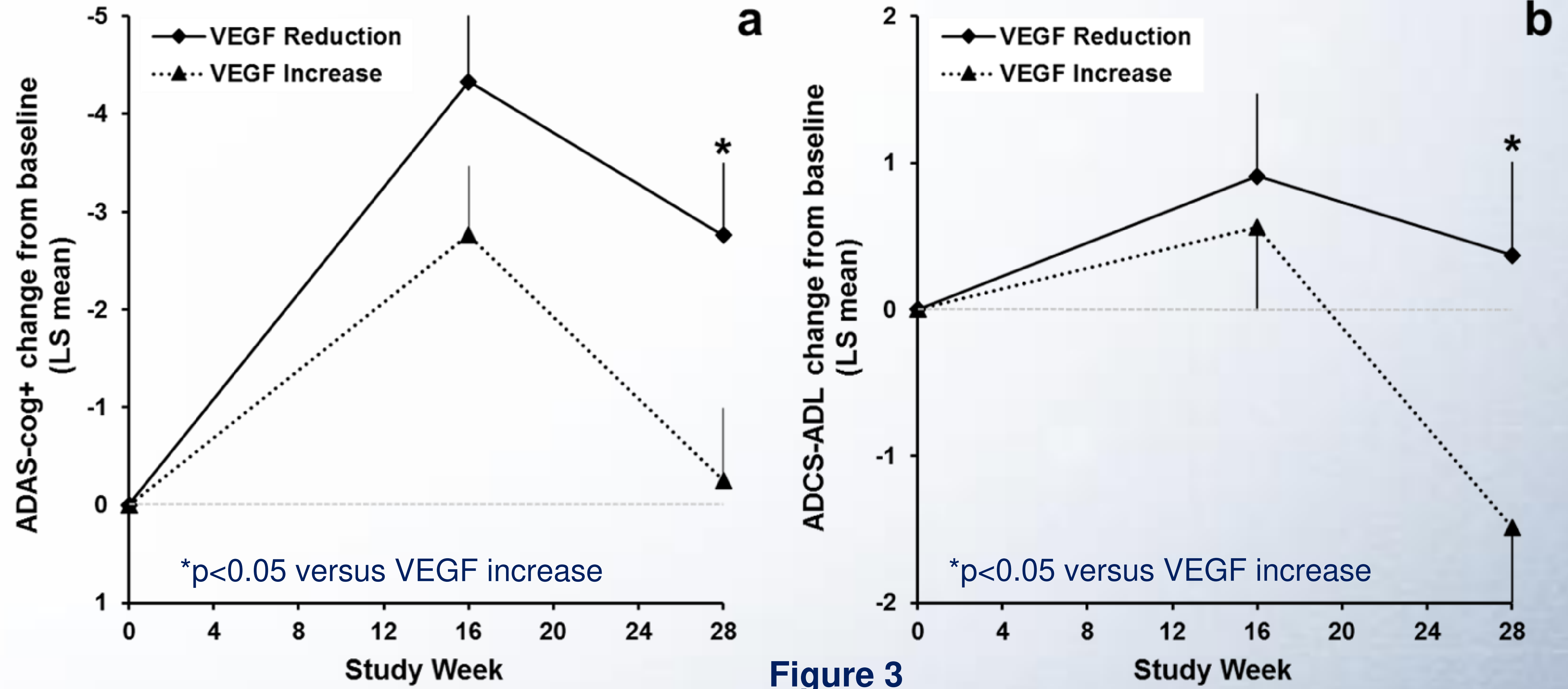
At study endpoint, VEGF reductions correlated with ADAS-cog+, and praxis and executive function ADAS-cog+ domain improvements in the total AD population (r=0.177, p=0.027; and r=0.184, p=0.021; respectively), and in APOE4 patients (r=0.253, p=0.027; and r=0.239, p=0.048; respectively); whereas correlations between VEGF reductions and functional improvements (ADCS-ADL) were only significant in APOE4 cases (r=-0.260, p=0.031).

CONCLUSIONS

Elevated baseline VEGF levels were associated with improved cognition-functioning in moderately-severe AD, but VEGF reductions at endpoint were found to be associated with treatment-induced cognitive-functional improvements particularly in APOE4 AD cases, and with better praxis and executive functions in advanced cases receiving Cerebrolysin plus donepezil. These findings are indicating the influence of VEGF on cognitive-functional performance and response to therapy in AD; and suggest that VEGF increases might represent a neuroprotective response in AD, especially in advanced and in APOE4 cases