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Rapid Communication

RAPID COMMUNICATION

Serum VEGF Predicts Clinical Improvement Induced by Cerebrolysin Plus Donepezil in Patients With Advanced Alzheimer's Disease

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Abstract

Serum vascular endothelial growth factor (VEGF) increases with Alzheimer's disease (AD) severity and may prevent cognitive decline. However, information on the influence of AD drug therapy on circulating VEGF is limited. This study assessed changes in serum VEGF levels and its association with clinical and functional responses in mild to moderate AD patients who were treated with Cerebrolysin, donepezil, or the combined therapy in a randomized, controlled trial. Treatment with Cerebrolysin plus donepezil reduced elevated serum VEGF levels and improved functioning and cognition significantly compared with donepezil alone in patients with advanced AD, and treatment differences were more pronounced in patients with higher VEGF levels. Our results indicate that the combined therapy reversed the increase of serum VEGF in advanced AD, which was associated with cognitive and functional responses, particularly in patients with high baseline VEGF.

Key Words: Alzheimer's disease (AD), vascular endothelial growth factor (VEGF), Cerebrolysin, donepezil, combined therapy

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Introduction

The angiogenic factor vascular endothelial growth factor (VEGF) has shown neuroprotective, neurotrophic, and cognitive effects in experimental conditions that might be relevant for the treatment of Alzheimer's disease (AD) patients. In AD mouse models, it was found that VEGF attenuated amyloid-beta (Aβ) burden and tau hyperphosphorylation, increased brain neurogenesis and angiogenesis, and ameliorated cognitive and memory impairment (Spuch et al., 2010; Wang et al., 2011; Religa et al., 2013; Garcia et al., 2014). Other studies demonstrated that VEGF prevented Aβ-induced endothelial apoptosis in vitro (Religa et al., 2013) and that blockade of VEGF receptor-1 protected hippocampal neurons against amyloid toxicity (Ryu et al., 2009). High-dose VEGF, however, decreased neuronal survival and negated the decrease in Aβ evoked by low-dose VEGF in cortical neurons (Sanchez et al., 2013).

We have recently found that serum VEGF increased with AD severity and that higher VEGF values were related to better memory and language performance in advanced AD patients carrying the Apolipoprotein E epsilon-4 (ApoE4) allele (Alvarez et al., 2018). Elevated levels of VEGF in cerebrospinal fluid (CSF) were also reported to be associated with less cognitive decline during aging, particularly in patients showing positive AD biomarkers (Hohman et al., 2015). However, changes in circulating VEGF and the interactions of VEGF with clinical responses after AD drug treatment have not been investigated in controlled clinical trials.

Cerebrolysin is a neuropeptide preparation that has shown clinical efficacy in mild to moderate AD patients (Alvarez et al., 2011a, 2011b; Gauthier et al., 2015). In these patients, Cerebrolysin reduced plasma tumor necrosis factor-alpha (TNF-α) concentrations (Alvarez et al., 2009) and enhanced serum brain-derived neurotrophic factor (BDNF) levels (Alvarez et al., 2016). Donepezil is a cholinesterase inhibitor that did not change circulating levels of VEGF in mild to moderate AD patients after 15-month therapy (Leyhe et al., 2009).

In the present study, we examined whether baseline VEGF and changes in VEGF levels after treatment with Cerebrolysin, donepezil, or a combined therapy were associated with cognitive and functional responses in AD patients included in a randomized controlled trial (Alvarez et al., 2011b).

Methods

This study assessed 158 patients with mild to moderate probable AD who completed the randomized controlled trial (clinicaltrials.gov no. NCT00911807) according to the protocol. Eligible patients had a Mini-Mental State Examination score between 12 and 25 and did not suffer from clinically significant depression. Written informed consent was obtained from all patients and caregivers before starting study procedures. This trial was conducted in accordance with the last version of the Declaration of Helsinki and with applicable regulatory requirements. The study protocol was approved by the Independent Ethics Committees of the 3 participating sites.

Patients received a double-dummy treatment with Cerebrolysin (10 mL, 5 i.v. infusions per week in weeks 1–4 and 13–16; n = 65), donepezil (5 mg once daily in weeks 1–4, and 10 mg once daily in weeks 5–28; n = 68), or a combined therapy of both (n = 67).

Blood samples for VEGF determinations were obtained at baseline, week 16 (end of Cerebrolysin treatment), and week 28 (study endpoint). Clinical evaluations were conducted at the same time points by using the AD Assessment Scale-cognitive subscale+ (ADAS-cog+) for cognition and the AD Cooperative Study-Activities of Daily Living Scale (ADCS-ADL) for functioning. In addition, the 14 individual items of the ADAS-cog+ were grouped and analyzed by the domains "memory and language" and "praxis and executive function" as previously studied (Alvarez et al., 2018). AD severity was graded on the 7-point Clinical Interview Based Impression of Severity with Caregiver Input scale (3 = mildly ill, 4 = moderately ill, 5 = markedly ill). In the ADAS-cog+, a lower score/negative score change indicates a better cognitive performance/improvement, and the opposite applies for ADCS-ADL.

Blood samples were taken in the morning using evacuated blood collecting tubes (Venojet, Terumo Europe N.V., Leuven, Belgium) and a butterfly-21 INT (Venisystems, Abbott Ireland Ltd., Sligo, Ireland) inserted into the antecubital vein. Serum samples were extracted and stored at –40°C until assay. Serum $VEGF^{165}$ levels were measured by an specific enzyme-linked immunosorbent assay kit (Alvarez et al., 2018).

VEGF data did not follow a normal distribution (Kolmogorov-Smirnov test); however, log-transformed VEGF data were normally distributed. Parametric statistics were used for analysis of VEGF natural log data. Group comparisons were conducted by chi-square and ANOVA analyses as appropriate. Treatment differences in VEGF natural log, ADAS-cog+, and ADCS-ADL responses at week 16 and 28 were analyzed by ANCOVA using scores of change from baseline as dependent variable and baseline scores as covariate with appropriate corrections for age, gender, platelet counts, disease severity, and ApoE4 status. Partial correlation analysis with corrections for age, gender, ApoE4, and/or disease severity was employed. Probability *P* values lower than .05 were considered statistically significant.

The estimation of the sample size has been made taking into account the primary endpoint (i.e., VEGF change from baseline). According to results of a previous study (Alvarez et al., 2018), it was calculated that 51 patients per arm in the total sample and 15 advanced AD cases per treatment group will allow to show significant treatment effects with 80% power for differences in average VEGF changes from baseline of 105 pg/mL and 175 pg/mL, respectively. With the same sample size, the power to detect treatment differences of 5 points in ADAS-cog+ change from baseline and of 4 points in ADCS-ADL change from baseline in advanced AD was around 80%.

Results and Discussion

Baseline serum VEGF concentrations and clinical characteristics were similar in all 3 treatment groups (Table 1).

Whereas there were no significant treatment effects on VEGF levels in mild to moderate AD patients, the combined therapy reduced serum VEGF elevations significantly vs donepezil in advanced, markedly ill AD cases at both week 16 (treatment difference: –0.515, 95% CI = –0.982/–0.047; *P* = .032) and week 28 (treatment difference: –0.654; 95% CI = –1.121/–0.188; *P* = .007) (Figure 1a).

The absence of a placebo group makes the interpretation of these results difficult. However, in 14 advanced AD cases not receiving any anti-dementia drug, we recently found an increase of serum VEGF over 6 months similar to that observed in donepezil-treated patients (X. A. Alvarez, unpublished data). As shown in Figure 1a, the expected increase in VEGF over time in advanced AD patients was reversed by the combined therapy and prevented by Cerebrolysin, while no effect was observed for donepezil. Given that average baseline VEGF concentrations were

Table 1. Effects of Cerebrolysin, Donepezil, and Combined Therapy on VEGF Serum Levels in AD Patients: Results and Baseline Clinical Characteristics

	Cerebrolysin	Donepezil	Combined therapy	Statistics		
All AD patients (n)	52	52	53[a]			
	Mean ± SD	Mean ± SD	Mean ± SD	*F*	*df*	*P*
Baseline VEGFnL (pg/mL)	5.33 ± 0.99	5.66 ± 0.82	5.53 ± 0.93	1.68	2	.189
Week-16 VEGFnL (pg/mL)	5.34 ± 1.06	5.66 ± 0.83	5.57 ± 0.87	1.66	2	.193
Week-28 VEGFnL (pg/mL)	5.22 ± 1.22[b]	5.74 ± 0.75	5.64 ± 0.83	4.28	2	.016
	n (%)	n (%)	n (%)	X^2	*df*	*P*
Female gender	38 (73.1)	40 (76.9)	43 (81.1)	0.96	2	.617
APOE ε4 allele	24 (46.2)	24 (46.2)	21 (39.6)	0.608	2	.738
CIBIS+	14 (26.9)	18 (34.6)	21 (39.6)	2.5	4	.642
3	22 (42.3)	20 (38.5)	16 (30.2)			
4	16 (30.8)	14 (26.9)	16 (30.2)			
5						
	Mean ± SD	Mean ± SD	Mean ± SD	*F*	*df*	*P*
Age (y)	74.65 ± 6.65	75.50 ± 7.43	72.89 ± 8.13	1.69	2; 154	.187
Platelets (×10⁹/L)	229.00 ± 68.01	223.79 ± 43.76	223.13 ± 57.72	0.16	2; 154	.849
MMSE (score)	17.27 ± 4.25	17.46 ± 4.27	17.75 ± 4.67	1.45	2; 154	.238
Baseline ADAS-cog+ (score)	41.15 ± 15.55	40.51 ± 16.21	39.79 ± 17.89	0.09	2; 154	.915
Baseline ADCS-ADL (score)	48.13 ± 19.73	52.62 ± 20.15	54.17 ± 19.95	1.29	2; 154	.278
Advanced AD (CIBIS+ 5; N)	16	14	16			
Baseline VEGFnL (pg/mL)	5.78 ± 0.64	5.46 ± 0.91	6.13 ± 0.77	2.77	2; 43	.074
Week-16 VEGFnL (pg/mL)	5.77 ± 0.70	5.88 ± 0.76	5.88 ± 0.63	0.13	2; 43	.878
Week-28 VEGFnL (pg/mL)	5.68 ± 0.82	5.86 ± 0.85	5.94 ± 0.82	0.41	2; 43	.663
	n (%)	n (%)	n (%)	X^2	*df*	*P*
Female gender	13 (81.3)	11 (78.6)	13 (76.5)	0.113	2	.945
APOE ε4 allele	8 (50.0)	8 (57.1)	3 (17.6)	5.896	2	.052
	Mean ± SD	Mean ± SD	Mean ± SD	*F*	*df*	*P*
Age (y)	75.94 ± 5.67	77.71 ± 7.26	74.81 ± 7.59	0.67	2; 43	.516
Platelets (×10⁹/L)	259.25 ± 78.01	234.14 ± 43.19	210.75 ± 75.12	2.02	2; 43	.145
MMSE (score)	12.62 ± 1.02	12.64 ± 1.01	13.25 ± 1.57	1.29	2; 43	.285
Baseline ADAS-cog+ (score)	61.06 ± 6.36	62.28 ± 7.63	60.74 ± 10.44	0.14	2; 43	.871
Baseline ADCS-ADL (score)	28.56 ± 15.99	31.43 ± 21.37	30.13 ± 13.32	0.11	2; 43	.899

Abbreviations: AD, Alzheimer's disease; ADAS-cog+, AD Assessment Scale-cognitive subscale plus; ADCS-ADL, AD Cooperative Study-Activities of Daily Living Scale; APOE e4, Apolipoprotein E epsilon 4 allele; CIBIS+, 7-point Clinical Interview Based Impression of Severity with Caregiver Input scale; MMSE, Mini-Mental State Examination; VEGFnL, VEGF natural log.

*a*Samples were not available for 1 case in the combined therapy group

*b**P* = .020 vs donepezil group (Bonferroni test).

higher in advanced cases than in milder cases (436 pg/mL vs 310 pg/mL; $P < .05$), combined therapy appears to "normalize" circulating VEGF in advanced AD. Mechanisms accounting for these treatment-related VEGF changes were not investigated, but the lack of treatment effects in mild to moderate AD suggests that VEGF changes in advanced AD are indirectly related to treatment.

Recently, we also found that combined therapy reduced plasma TNF-α significantly compared with donepezil in advanced AD cases, and this decrease was 3 times greater in patients with higher baseline VEGF than in those with lower baseline VEGF, defined as above or below median VEGF serum level (Alvarez, data not published). Similarly, in the present study, the reduction of VEGF induced by combined therapy was also double in higher VEGF than in lower VEGF cases (treatment differences: –462.64 pg/mL and –240.66 pg/mL, respectively). Since TNF-α stimulates VEGF production in human monocytes/macrophages (Haneda et al., 2011), decreases in circulating TNF-α might account for or contribute to reductions in serum VEGF. Of note, in agreement with our observation, it has been reported that anti-TNF-α therapy was more effective in Crohn's disease patients with elevated serum VEGF (Eder et al., 2015).

Cerebrolysin was shown to reduce elevated serum levels of TNF-α in AD (Alvarez et al., 2009) and might contribute to prevent VEGF elevations also by reducing brain Aβ load (Rockenstein et al., 2006), by increasing the glucose transporter-1 levels (Gschanes et al., 2000), and/or by enhancing BDNF expression (Rockenstein et al., 2015; Alvarez et al., 2016) since all of these mechanisms are involved in VEGF upregulation (Wood et al., 2015; Jais et al., 2016; Cho et al., 2017). In addition, the synergistic action of Cerebrolysin plus donepezil to enhance serum BDNF in AD patients (Alvarez et al., 2016) might also account for the reversal of the VEGF increase. All these mechanisms might contribute to the indirect influence of combined therapy on VEGF in advanced AD.

Combined therapy also improved cognitive (Figure 1b) and functional (Figure 1c) performance in advanced AD patients. Changes from baseline resulted in significant treatment

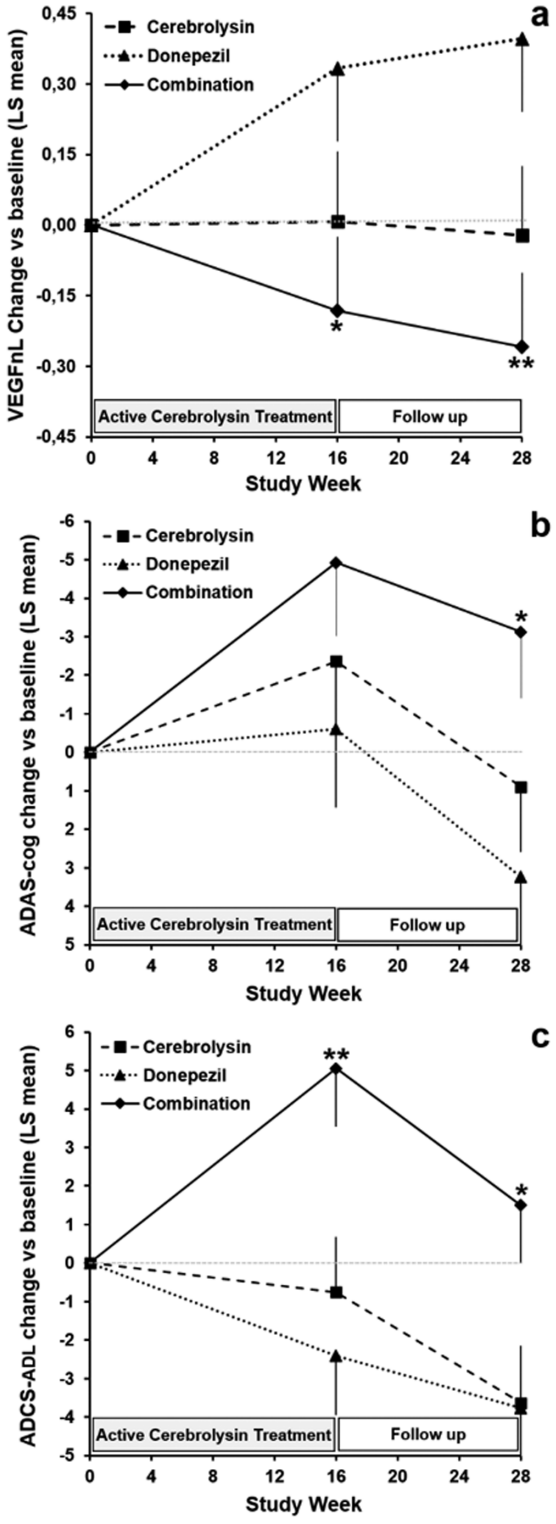

Figure 1. Effects of Cerebrolysin, donepezil and the combination therapy on: (a) serum VEGF levels (VEGFnL: vascular endothelial growth factor natural log), (b) cognitive performance (ADAS-cog+: AD Assessment Scale-cognitive subscale plus), and (c) functioning (ADCS-ADL: AD Cooperative Study-Activities of Daily Living Scale) at week 16 (end of active Cerebrolysin treatment) and at week 28 (end of the study) in patients with advanced Alzheimer's disease (AD). (a) *P < .05 and **P < .01 versus donepezil group; (b) *P < .05 versus Donepezil group; (c) *P < .05 and **P < .01 vs donepezil and Cerebrolysin groups. Data are presented as LS mean (± SE).

differences vs donepezil of –6.34 points ($P = .017$) at week 28 in the ADAS-cog+ and of 7.46 ($P = .002$) and 5.28 ($P = .024$) points at weeks 16 and 28 in the ADCS-ADL functioning.

Although significant clinical improvements with respect to placebo have been found with donepezil 10 mg (Gauthier et al., 2002) and with Cerebrolysin 10 mL (Alvarez et al., 2011a) in advanced AD, data presented here show for the first time, to our knowledge, superiority of the combination over monotherapy. This synergistic effect of Cerebrolysin and donepezil on cognition and functioning was not evident in mild to moderate stages (Alvarez et al., 2011b) and might indicate a delay in clinical deterioration (Figure 1b, c) and probably disease progression in advanced AD patients.

The involvement of VEGF in the positive clinical outcome of advanced AD patients is supported by the fact that treatment differences were larger than average in cases with higher baseline VEGF for ADAS-cog+ at week 28 (–9.83 points) and for ADCS-ADL at week 16 (9.19 points) and week 28 (7.28 points). Results of partial correlation analysis also indicate that higher baseline VEGF levels are associated with better cognitive performance in ADAS-cog+ and in its memory and language domain at week 16 ($r = –0.561$, $P = .000$; and $r = –0.485$, $P = .001$; respectively) and at week 28 ($r = –0.435$, $P = .003$; and $r = –0.338$, $P = .027$, respectively); with cognitive improvements in total ADAS-cog+ and in memory and language at week 16 ($r = –0.435$, $P = .003$; and $r = –0.493$, $P = .001$) and at week 28 ($r = –0.323$, $P = .032$; and $r = –0.337$, $P = .027$); and with functional improvement at week 16 ($r = 0.313$, $P = .039$). Correlations between baseline VEGF and clinical parameters were more obvious in patients treated with Cerebrolysin alone or plus donepezil than in cases receiving donepezil monotherapy. According to these results, elevated baseline VEGF levels predict a better clinical response to treatment, particularly with Cerebrolysin, in advanced AD patients. This finding is in agreement with results of previous clinical investigations showing an attenuated decline of memory and executive function in patients with elevated CSF levels of VEGF and positive AD biomarkers (Hohman et al., 2015) and an association of serum VEGF with better memory and language in advanced ApoE4 patients (Alvarez et al., 2018). Negative associations of CSF levels of VEGF with whole-brain atrophy in amyloid-positive individuals (Paterson et al., 2014) and with hippocampal atrophy in patients with prominent AD biomarkers (Hohman et al., 2015) suggest a neuroprotective effect of VEGF as the underlying mechanism.

The relevance of VEGF for the observed treatment effects in advanced AD, however, appears controversial. On the one hand, the best clinical response was obtained in patients treated with combined therapy. Furthermore, decreases in VEGF levels at week 28 correlated significantly with improvements in ADAS-cog+ praxis and executive function domain ($r = 0.382$, $P = .011$). In the total study population and after adjustments for disease severity, correlations between reductions in VEGF levels and clinical improvements at week 28 were also significant in all patients treated with Cerebrolysin (ADAS-cog+: $r = 0.357$, $P = .000$; memory and language: $r = 0.268$, $P = .006$; praxis and executive function: $r = 0.317$, $P = .001$; ADCS-ADL: $r = –0.231$, $P = .018$). These data, together with the finding of greatest treatment effects in patients with high VEGF levels, suggest that the reduction of excessive VEGF levels might have caused at least in part the observed clinical improvement. In fact, high serum VEGF was associated with an accelerated cognitive decline (Chiapelli et al., 2006), clinical severity, and rapid progression to the advanced disease stage (Alvarez et al., 2018). Excessively high VEGF could

even have a neurotoxic effect as shown in neuronal cell cultures by the reduction of survival and the abolition of decreases in Aβ induced by low doses of VEGF (Sanchez et al., 2013). Finally, we cannot exclude the possibility that high VEGF levels represent an endogenous reaction to counteract pathogenic alterations (TNF-α, Aβ, BDNF) and therefore the decrease of VEGF is reflecting changes induced by combined therapy in these molecules rather than having a direct therapeutic contribution.

In summary, the present results indicate that (1) the combined therapy reverses increased levels of serum VEGF and has a significant treatment effect on cognition and functioning compared with donepezil monotherapy in advanced AD; (2) the reductions of high serum VEGF levels correlate with clinical responses; and (3) higher baseline VEGF levels are associated with greater treatment effects on VEGF and clinical parameters. These findings need to be confirmed in larger placebo-controlled clinical trials since the lack of a placebo group and the small sample size are the main limitations of our study. Future research addressing the interactions of peripheral AD biomarkers (particularly Aβ, tau, and TNF-α) and soluble VEGF receptors with serum VEGF may help to further pinpoint the influence of VEGF on clinical functioning and therapeutic responses in AD.

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Statement of Interest

The authors declare no conflicts of interest.

X. A. Alvarez was principal investigator in clinical trials and other research projects granted by EVER Neuro Pharma GmbH and a speaker in EVER Neuro Pharma GmbH-sponsored symposia. S. Winter is an employee of EVER NeuroPharma GmbH. D. F. Muresanu was principal investigator in several clinical trials with Cerebrolysin and is a member of the CAPTAIN trial scientific advisory board. H. Moessler is a scientific advisor for EVER NeuroPharma GmbH.

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