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ORIGINAL RESEARCH ARTICLE

Benefits of Treatment with *Ginkgo Biloba* Extract EGb 761 Alone or Combined with Acetylcholinesterase Inhibitors in Vascular Dementia

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Abstract

Background Vascular dementia (VaD) is the most severe manifestation of cognitive impairment caused by cerebrovascular disease. There are currently no specific drug treatments approved for VaD, with cholinesterase inhibitors (AChEI) being frequently used in VaD. However, the benefits they provide are small and short-lived. The standardized extract of *Ginkgo biloba* EGb 761 has demonstrated protective properties against neuronal and vascular damage and has been used as a pharmacological treatment for VaD.

Objectives This study aims to study the efficacy of EGb 761 alone and in combination with AChEI in a real-life setting. We carried out a retrospective analysis of data over a 12-month period in a sample of people suffering from VaD.

Methods We retrospectively identified 77 patients with a diagnosis of VaD who had received treatment with any of the following drugs: *Ginkgo biloba* extract EGb 761 (240 mg daily), donepezil (10 mg daily), galantamine (16 or 24 mg daily), or rivastigmine patch (9.5 or 13.3 mg daily). Subjects were divided into three groups according to the treatment they had received: EGb 761 alone ($n = 25$), AChEI alone ($n = 26$), and EGb 761+AChEI ($n = 26$). Cognitive functioning was assessed by Mini-Mental State Examination (MMSE), Rey Auditory Verbal Learning Test (RAVLT), Symbol Digit Modalities Test (SDMT), Boston Naming Test (BNT), Trail Making Test forms A (TMTA) and B (TMTB), Letter (LFT) and Category Fluency Test (CFT); neuropsychiatric symptoms were assessed by the Neuropsychiatric Inventory (NPI); functional capacity was assessed by Interview for Deterioration in Daily Living (IDDD).

Results A statistically significant improvement was observed in the EGb 761 group versus the AChEI group at 12 months' follow-up in CFT (+1.74, $p < 0.001$), TMTA (−17.91, $p = 0.031$) and NPI (−5.89, $p < 0.001$). With regard to the combined treatment, a statistically significant improvement was shown in the EGb 761 plus AChEI treatment group versus AChEI group at the 12-month follow-up in MMSE (+2.0, $p = 0.001$), RAVLT (+2.23, $p = 0.007$), CFT (+1.15, $p = 0.013$), TMTA (−19.92, $p = 0.012$), TMTB (−46.50, $p < 0.001$) and NPI (−6.77, $p < 0.001$). In the same line, a statistically significant improvement was observed in the EGb 761 plus AChEI treatment group versus EGb 761 at 12-month follow-up regarding MMSE (+2.11, $p = 0.001$), RAVLT (+2.35, $p = 0.004$) and TMTB (−25.25, $p = 0.015$).

Conclusion After 12 months of treatment EGb 761 alone or combined with AChEI showed cognitive and behavioral benefits in patients suffering from VaD. This study thus provides additional real-world evidence for the combined use of EGb 761 and anti-dementia drugs in VaD patients.

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Key Points

In this retrospective study, the *Ginkgo biloba* extract EGb 761 showed cognitive and behavioral benefits in vascular dementia.

The benefits increased when EGb 761 and acetylcholinesterase inhibitors were used in combined treatment.

This study serves as a model for long-term randomized controlled trials.

1 Introduction

Cognitive impairment of vascular etiology is the second most common cause of clinically diagnosed dementia after Alzheimer disease (AD) and accounts for at least 20% of all dementia cases [1, 2]. The term vascular cognitive impairment (VCI) is currently widely accepted to describe a broad spectrum of cognitive impairments caused by cerebrovascular disease with vascular dementia (VaD) being its most severe manifestation [3, 4].

In a revised conceptualization of VCI, the Vascular Impairment of Cognition Classification Consensus Study (VICCCS) classified VCI into mild and major subtypes according to the level of impairment [5]. Mild VCI is not subdivided, but major VCI (or VaD) has four subdivisions: post-stroke dementia, subcortical ischemic vascular dementia, multi-infarct (cortical) dementia, and mixed dementias. The VICCCS sets as consensus for the definition of VaD the presence of clinically significant deficits in at least one cognitive domain (other deficits may be present in multiple domains) and severe disruption to instrumental activities of daily living (independent of the motor/sensory sequelae of the vascular event). In addition, imaging evidence of cerebrovascular disease is considered another requirement for VaD [6].

The epidemiology of VaD varies widely between studies due to numerous factors, such as the assessment protocols used, the heterogeneity of pathophysiological factors involved, the diagnostic criteria used, the age of affected individuals or the presence of comorbidities [7–9]. In a population-based study, the incidence of vascular dementia was 0.1 per 1000 person-years in people aged 60–64 years, increasing with age to 7.0 per 1000 person-years in people aged 90–94 years, with a higher risk of vascular dementia in men [10]. Results of some studies show that among stroke survivors, VCI is present in more than 60% at 3 months after stroke [11] and one-third of all stroke survivors developed dementia between 1 and 3 years after stroke [12, 13], especially if blood circulation in the hippocampus and prefrontal areas was severely impaired. A population-based study analyzing autopsies of dementia cases found that 13% had pure vascular dementia and a further 12% showed the presence of a significant vascular contribution to the pathology, implying that vascular disease was a major component in at least 25% of dementia cases [14].

There are currently no specific drug treatments recommended for VaD. Cholinesterase inhibitors (AChEI) are widely used in AD but may also be useful in people with VaD [15–17]. However, the benefits they provide are small and short-lived [18–21]. The results from a recent Cochrane review found moderate- to high-certainty evidence that AChEI has a slight beneficial effect on cognition in people with VaD, although the size of the change is unlikely to be clinically important. The data suggest that donepezil has the greatest effect on cognition, but at the cost of adverse effects [22].

The standardized extract of *Ginkgo biloba* EGb 761 has shown protective properties against neuronal and vascular damage and has been used as a pharmacological treatment for VaD [23, 24]. The results of a recent systematic review that evaluated randomized controlled trials of the *Ginkgo biloba* extract EGb 761 in the treatment of patients diagnosed with VaD, according to the criteria of the National Institute for Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neuroscience criteria [25] have confirmed that EGb 761 can effectively enhance cognitive levels and behavioral and psychological symptoms of VaD patients [26]. The European Medicines Agency (EMA) supports its use to improve the age-related cognitive impairment (worsening of mental abilities) and quality of life of adults with mild dementia, and it is recommended in some guidelines for the treatment of cognitive disorders [27–29].

The *Ginkgo biloba* extract EGb 761 contains flavonoids, terpene lactones, and various other constituents [30]. Egb 761 has a positive effect on cognitive and neurological function based on the improvement of vascular flow, antioxidant effect, anti-inflammatory action, antiapoptotic action, enhancing neuroplasticity, modulation of amyloid-aggregation, and the defense against mitochondrial dysfunction, which would confer neuroprotective properties [31–35]. Egb 761 has been shown to produce cognitive improvement in both AD and VaD [36, 37]. Overall, the combination treatment supporting the combination of EGb 761 with AChEIs for the treatment of VaD has been insufficiently investigated. For AD, a pilot study showed only a trend towards enhanced benefit of the combined treatment, but a better tolerability of the combined treatment compared to AChI alone [38], and in a non-placebo-controlled, but large observational study, a significant benefit of combined treatment compared to AChI

alone was shown [39]. Thus, since there may be a future role for combination therapy, further evidence is needed to evaluate the role of EGb 761 as an add-on therapy to standard AChEIs treatment.

This study aimed to investigate the efficacy of EGb 761 alone and in combination with AChEI in a real-life setting.

2 Methods

2.1 Patients Selection

We retrospectively identified patients with a diagnosis of VaD who attended the Alzheimer Disease Center and Memory Clinic of the Instituto Andaluz de Neurociencia (IANEC), Málaga, Spain, between January 2018 and December 2020. In this research we studied patients suffering from VaD according to the VICCCS guideline definition, which includes four subdivisions: post-stroke dementia, subcortical ischemic vascular dementia, multi-infarct (cortical) dementia, and mixed dementias [6].

The diagnosis of VaD had been recorded on each participant's medical history issued by a neurologist, neuropsychologist, or psychiatrist. All selected participants were required to allow collection of their medical history, including treatment with EGb 761 or AChEi alone or combined with both drugs, physical examination, neurological and psychiatric examination, neuropsychological assessment, and magnetic resonance imaging (MRI). As part of the routine clinical follow-up at the IANEC, patients with a diagnosis of VaD are evaluated at baseline and every 6 months. Information on demographic and clinical characteristics are collected. At the study inclusions visit, data were recorded regarding: sex, age, educational level, VaD diagnosis, personal and family history, personal psychiatric history, general medication, and antidementia drugs.

The exclusion criteria were: the presence of focal neurological signs other than those caused by VaD itself, patients with epilepsy or inflammatory brain disease, severe psychiatric disorders or substance abuse, absence of a reliable informant, absence of a complete medical history to assess the study variables, and presence of a sensory disorder (e.g., severe vision and hearing impairment).

Vascular dementia subjects who received treatment for 12 months with any of the following drugs and doses were considered as candidates: EGb 761 (240 mg daily), donepezil (5 or 10 mg daily), galantamine (16 or 24 mg daily), or rivastigmine patch (9.5 or 13.3 mg daily). Subjects were divided into three groups according to the treatment they had received: EGb 761 only, AChEI only or EGb 761 plus AChEI.

During the study period, a total of 194 patients with VaD were identified. From these 194 subjects, 32 potential participants were excluded because they had insufficient documentation in their medical record, 23 could not be contacted, 19 refused to participate in the study, or meet exclusion criteria ($n = 43$).

The sample size in this retrospective study was not ascertained a priori. The study was approved by the ethics committee of the Instituto Andaluz de Neurociencia, Málaga, Spain; and an informed consent was obtained from patients or their representative caregivers.

2.2 Assessment

Drug effects on cognition, behavior, and functional performance were evaluated at baseline, 6, and 12 months using the following neuropsychological tests:

The Mini-Mental State Examination (MMSE) is the most commonly used test for the screening of cognitive functioning. Possible scores range from 0 to 30 points, where higher scores indicate better cognitive function [40].

The Rey Auditory Verbal Learning Test (RAVLT) is a verbal list-learning and memory test to assess verbal episodic memory. The RAVLT consists of 5 repeated learning trials of the same 15-word list, with immediate and delayed recall trials after 3 and 30 min, respectively, as well as recognition tests. In this study we used the total sum of words recalled across the five trials to measure total encoding [41].

The Symbol Digit Modalities Test (SDMT) is a widely used measure of information processing speed. The subject is presented with a page headed by a key that pairs the single digits 1–9 with nine symbols. Rows below contain only symbols, and the subject's task is to write or orally report the correct number in the spaces below. After completing the first 10 items with guidance, the subject is timed to determine how many responses can be made in 90 s [42].

The Boston Naming Test (BNT) is the best-known neuropsychological test used widely for evaluating linguistic ability, which includes object naming and word retrieval. In this study we used the abbreviated 15-item version [43].

The Trail Making Test is a tool that is used for the assessment of the ability to flexibly switch attention between competing task-set representations. The TMT comprises two task components, TMT-A and TMT-B. The TMT-A requires the participant to draw lines and connect circled numbers in a numerical sequence. In the TMT-B, the participant is asked to draw lines to connect circled numbers and letters in an alternating numeric and alphabetic sequence. The participant is instructed to complete both task components as fast and accurately as possible without lifting the pen from the worksheet [44].

Letter fluency test (LFT), and Category fluency test (CFT) were used to assess verbal fluency. Both involve the activation of multiple cognitive processes engaging verbal knowledge and executive function to inhibit repetitions. In

the LFT, subjects were instructed to say as many words as possible that begin with the letter 'P' for 1 minute. In the CFT, the subjects were asked to list as many animals as possible within 1 min [45].

The assessment of behavioral and psychological symptoms of dementia (BPSD) was carried out using the Neuropsychiatric Inventory (NPI). The NPI is composed of 12 subscales that evaluate the most commonly occurring BPSD in AD patients. A composite score for each subscale was obtained by multiplying frequency by severity, with a maximum of 12 points. A total NPI composite score can be obtained ranging from 0 to 144 points [46].

The patients' performance on activities of daily life was assessed using the Interview for Deterioration in Daily Living (IDDD). Possible scores range from 33 to 99 points, where higher scores indicate worse functional ability [47].

2.3 Statistical Analysis

Demographic variables were reported using the mean, standard deviation, number, and percentage. Baseline differences between treatment groups were assessed by Analysis of Variance (ANOVA) and nonparametric tests, as appropriate.

The efficacy of each of the treatment groups was assessed by ANOVA for Repeated Measures with three repeated measures: at the treatment inclusion visit, at 6 months, and at 12 months, controlling for demographic and clinical characteristics that approached significance on univariate analysis. Efficacy was determined by the change in cognitive, neuropsychiatric, and functional assessment scores from baseline to Month 12. Differences between the treatment groups were assessed using an Analysis of Covariance (ANCOVA) with Bonferroni correction for multiple comparisons.

All analyses were conducted with SPSS Statistics (Version 25.0) and the significance level was set at $p = 0.05$.

3 Results

A total of 77 patients met the inclusion criteria and their data were available for analysis (43 female, 34 male). Patients had a mean age of 76.13±5.57 years (range 65–95) and mean years of education of 6.48±1.86 (range 4–15). At baseline, patients treated with EGb 761 only ($n = 25$) did not differ from those treated with AChEI only ($n = 26$) or with EGb 761 plus AChEI ($n = 26$) (Table 1).

According to the VICCCS criteria 12 (15.58%) patients suffered from post-stroke dementia, 21 (27.27%) patients showed subcortical ischemic vascular dementia, 15 (19.49%) patients suffered from multi-infarct (cortical) dementia and 29 (37.66%) showed mixed dementia. There were no statistically significant differences between the four groups in relation to the demographic variables.

3.1 Changes in Cognitive, Behavioral and Functional Scores from Baseline to Endpoint

The results of Repeated Measures ANOVA showed that the EGb 761 treatment group yielded significant baseline-to-endpoint increases in MMSE (+1.40, $p < 0.0001$), RAVLT (+1.36, $p < 0.0001$), CFT (+3.84, $p < 0.0001$), LFT (+2.68, $p < 0.0001$), BNT (+3.16, $p < 0.0001$) and SDMT (+13.96, $p < 0.0001$). Similarly, the EGb 761 group showed significantly baseline-to-endpoint reduction in TMTA (−21.32, $p < 0.0001$), TMTB (−85.48, $p < 0.0001$) and NPI (−14.68, $p < 0.0001$) (Table 2). The IDDD for the EGb 761 group did not reach statistical significance ($p = 0.767$) (Table 2).

The results of Repeated Measures ANOVA showed that the AChEI treatment group rendered significant baseline-to-endpoint increases in MMSE (+1.26, $p < 0.0001$), RAVLT (+1.53, $p < 0.0001$), CFT (+2.23, $p < 0.0001$), LFT (+2.19, $p < 0.0001$), BNT (+4.0, $p < 0.0001$) and SDMT (+13.46, $p < 0.0001$). In the same line, the AChEI group showed significantly baseline-to-endpoint reduction in TMTA (−7.38, $p < 0.0001$), TMTB (−50.38, $p < 0.0001$) and NPI (−11.15, $p < 0.0001$). The IDDD score for the AChEI group did not reach statistical significance ($p = 0.153$) (Table 2).

The results of Repeated Measures ANOVA showed that the EGb 761 plus AChEI combined group yielded significant baseline-to-endpoint increases in MMSE (+3.46, $p < 0.0001$), RAVLT (+3.80, $p < 0.0001$), CFT (+3.19, $p < 0.0001$), LFT (+3.0, $p < 0.0001$), BNT (+2.61, $p < 0.0001$) and SDMT (+7.15, $p < 0.0001$). Likewise, the EGb 761 plus AChEI combined group showed significant baseline-to-endpoint reduction in TMTA (−26.03, $p < 0.0001$), TMTB (−107.80, $p < 0.0001$) and NPI (−18.26, $p < 0.0001$). The IDDD score for EGb 761 plus AChEI group did not reach statistical significance ($p = 0.929$) (Table 2).

3.2 Changes in Cognitive, Behavioral, and Functional Scores Between Treatment Groups

A statistically significantly larger improvement was observed in the EGb 761 group versus AChEI group on CFT at both 6 ($p = 0.005$) and 12 months ($p < 0.001$), TMTA at 12 months ($p = 0.031$) and NPI at both 6 ($p < 0.001$) and 12 months ($p < 0.001$) (Table 3, Fig. 1).

A statistically significant improvement was observed in the EGb 761 plus AChEI treatment group versus the AChEI group regarding MMSE scores at both 6 ($p = 0.005$) and 12 months ($p = 0.001$), RAVLT at 12 months ($p = 0.007$), CFT at 12 months ($p = 0.013$), TMTA at 12 months ($p = 0.012$), TMTB at 12 months ($p < 0.001$) and NPI at both 6 and 12 months ($p < 0.001$) (Table 3, Fig. 1).

Table 1 Demographic and clinical characteristics of patients at baseline

Variable	Overall ($n=77$)	EGb 761 ($n=25$)	AChEI ($n=26$)	EGb 761+AChEI ($n=26$)	p-value ANOVA/ χ^2
Age	76.13±5.57	75.96±5.84	76.62±6.94	75.67±3.70	0.833
Sex					
Female	43 (55.8)	11 (44.0)	11 (42.3)	21 (80.8)	0.067
Male	34 (44.2)	14 (56.0)	15 (57.7)	5 (19.2)	
Marital status					
Married	28 (36.4)	11 (44.0)	10 (38.5)	7 (26.9)	0.931
Single/divorced	8 (10.4)	1 (4.0)	3 (11.5)	4 (15.4)	
Widowed	41 (53.2)	13 (52)	13 50.0)	15 (57.7)	
Duration of dementia (months)	30.68±10.75	29.84±10.75	34.01±12.44	28.25±8.09	0.147
Education (years)	6.48±1.86	6.68±2.03	6.35±2.02	6.38±1.58	0.788
MMSE	20.90±2.22	20.80±2.22	21.04±1.91	20.85±2.57	0.914
RAVLT	18.47±2.95	18.52±2.89	18.46±3.29	18.42±2.76	0.986
CFT	8.49±0.94	8.52±0.92	8.38±0.75	8.58±1.14	0.755
LFT	8.81±1.10	8.76±1.05	8.77±1.03	8.88±1.24	0.995
TMTA	163.90±22.63	161.64±25.13	165.62±21.59	164.35±21.80	0.812
TMTB	242.34±29.12	248.00±29.35	234.15±30.49	245.08±26.67	0.220
SDMT	21.79±9.13	21.04±10.59	22.08±7.28	22.23±9.59	0.783
BNT	8.90±2.75	9.20±2.31	8.27±2.89	9.24±2.97	0.228
NPI	27.19±6.87	25.48±6.75	27.85±7.39	28.19±6.38	0.253
IDDD	50.95±11.75	48.44±10.94	52.81±13.32	50.50±10.81	0.399

Values are mean ± SD or number (%)

ANOVA analysis of variance, *BNT* Boston Naming Test, CFT Category Fluency Test, χ^2 Chi-square, *IDDD* Interview for Deterioration in Daily Living Activities in Dementia, *LFT* Letter Fluency Test, *MMSE* Mini Mental State Examination, *NPI* Neuropsychiatric Inventory, *RAVLT* Rey Auditory Verbal Learning Test, *SDMT* Symbol Digit Modalities Test, *TMTA* Trail Making Test part A, *TMTB* Trail Making Test part B

Consistent with the aforementioned results, a statistically significant improvement was observed in the EGb 761 plus AChEI treatment group versus EGb 761 group regarding MMSE scores at both 6 ($p = 0.01$) and 12 months ($p = 0.001$), RAVLT at 12 months ($p = 0.004$) and TMTB at 12 months (p = 0.015) (Table 3, Fig. 1).

3.3 Safety Analysis

The overall incidence of patients reporting adverse events throughout the study that were considered possibly related to treatment was 26.5% in the EGb 761 group, 52% in the AChEI group and 41.2% in the EGb 761 plus AChEI group. Table 4 shows the adverse events reported in the three groups; the most commonly reported were insomnia (12%) and headache (12%) for EGb 761; dizziness (23.07%), diarrhea (23.07%), skin rashes (23.07%), fatigue (19.23%) and headaches (19.23%) for the AChEI group and dizziness (23.07%) and skin rashes (19.23%) in the combined treatment group.

Most of adverse events in all the three groups were transient, were of mild-to-moderate intensity, and resolved spontaneously. No deaths or serious adverse events occurred during the study. Clinically relevant changes over time or differences between treatment groups were not observed in clinical laboratory test results, vital signs, weight, or ECG parameters.

4 Discussion

In this retrospective study, treatment with *Ginkgo biloba* extract EGb 761 for 12 months alone or in combination with AChEI was well tolerated and was associated with a reduction in cognitive impairment and neuropsychiatric burden in patients with VaD. These results are particularly relevant, especially considering that there are currently not many pharmacological treatments approved for improving either cognition or function in people with VaD.

In our study, in terms of improved cognitive performance and neuropsychiatric symptoms, EGb 761 alone showed significantly superior efficacy to AChEI alone, in CFT, TMTA and NPI scores. The positive response seen in the EGb 761 alone group is consistent with previous results. Indeed,

Table 2 Rating scale score within-treatment changes

Variable	T0	T1	T2	Difference (T0–T2)	*p*-value[a] ANCOVA
MMSE					
EGb 761	20.80±2.22	21.72±2.03	22.20±2.10	1.40	0.001
AChEI	21.04±1.91	21.62±2.14	22.31±2.31	1.27	<0.0001
EGb 761+AChEI	20.85±2.57	23.27±1.18	24.31±1.32	3.46	<0.0001
RAVLT					
EGb 761	18.52±2.89	18.96±2.75	19.88±2.45	1.36	<0.0001
AChEI	18.46±3.29	18.92±3.04	20.00±2.86	1.54	<0.0001
EGb 761+AChEI	18.42±2.76	18.50±2.53	22.23±2.89	3.81	<0.0001
CFT					
EGb 761	8.52±0.92	9.84±1.79	12.36±1.49	3.84	<0.0001
AChEI	8.38±0.75	8.65±0.89	10.62±1.17	2.23	<0.0001
EGb 761+AChEI	8.58±1.14	9.04±0.99	11.77±1.53	3.19	<0.0001
LFT					
EGb 761	8.76±1.05	9.68±1.21	11.44±1.58	2.68	<0.0001
AChEI	8.77±1.03	9.85±1.29	10.96±1.37	2.19	<0.0001
EGb 761+AChEI	8.88±1.24	10.12±1.53	11.88±1.79	3.00	<0.0001
TMTA					
EGb 761	161.64±25.13	150.20±24.80	140.32±23.99	−21.32	<0.0001
AChEI	165.62±21.59	162.42±24.73	158.23±27.38	−7.38	<0.001
EGb 761+AChEI	164.35±21.80	151.08±22.11	138.31±20.96	−26.04	<0.0001
TMTB					
EGb 761	248.00±29.35	196.84±35.03	162.52±32.01	−85.48	<0.0001
AChEI	234.15±30.49	191.23±39.76	188.77±41.09	−50.38	<0.0001
EGb 761+AChEI	245.08±26.67	195.15±26.11	137.27±14.01	−107.81	<0.0001
SDMT					
EGb 761	21.04±10.59	28.28±9.83	35.00±7.86	13.96	<0.0001
AChEI	22.08±7.28	28.15±8.36	35.34±8.33	13.46	<0.0001
EGb 761+AChEI	22.23±9.59	23.42±10.40	29.38±11.37	7.15	<0.0001
BNT					
EGb 761	9.20±2.31	10.80±1.50	12.36±1.32	3.16	<0.0001
AChEI	8.27±2.89	10.81±1.17	12.27±1.12	4.00	<0.0001
EGb 761+AChEI	9.24±2.97	11.12±1.48	11.85±1.29	2.61	0.002
NPI					
EGb 761	25.48±6.75	15.80±6.02	10.80±5.59	−14.68	<0.0001
AChEI	27.85±7.39	21.54±5.60	16.69±4.48	−11.15	<0.0001
EGb 761+AChEI	28.19±6.38	14.85±4.78	9.92±3.25	−18.27	<0.0001
IDDD					
EGb 761	48.44±10.94	47.32±10.29	49.20±11.88	0.76	0.767
AChEI	52.81±13.32	50.96±10.25	55.00±14.02	2.19	0.153
EGb 761+AChEI	50.50±10.81	52.46±13.46	51.51±10.16	1.01	0.929

Values are mean ± SD

[a]P-values refer to changes from baseline to Month 12

T0 baseline, *T1* follow-up 6 months, *T2* follow-up 12 months

ANCOVA analysis of covariance, *BNT* Boston Naming Test, *CFT* Category Fluency Test, χ^2 Chi-square, *IDDD* Interview for Deterioration in Daily Living Activities in Dementia, *LFT* Letter Fluency Test, *MMSE* Mini Mental State Examination, *NPI* Neuropsychiatric Inventory, *RAVLT* Rey Auditory Verbal Learning Test, *SDMT* Symbol Digit Modalities Test, *TMTA* Trail Making Test part A, *TMTB* Trail Making Test part B

Table 3 Rating scale score changes between treatment groups

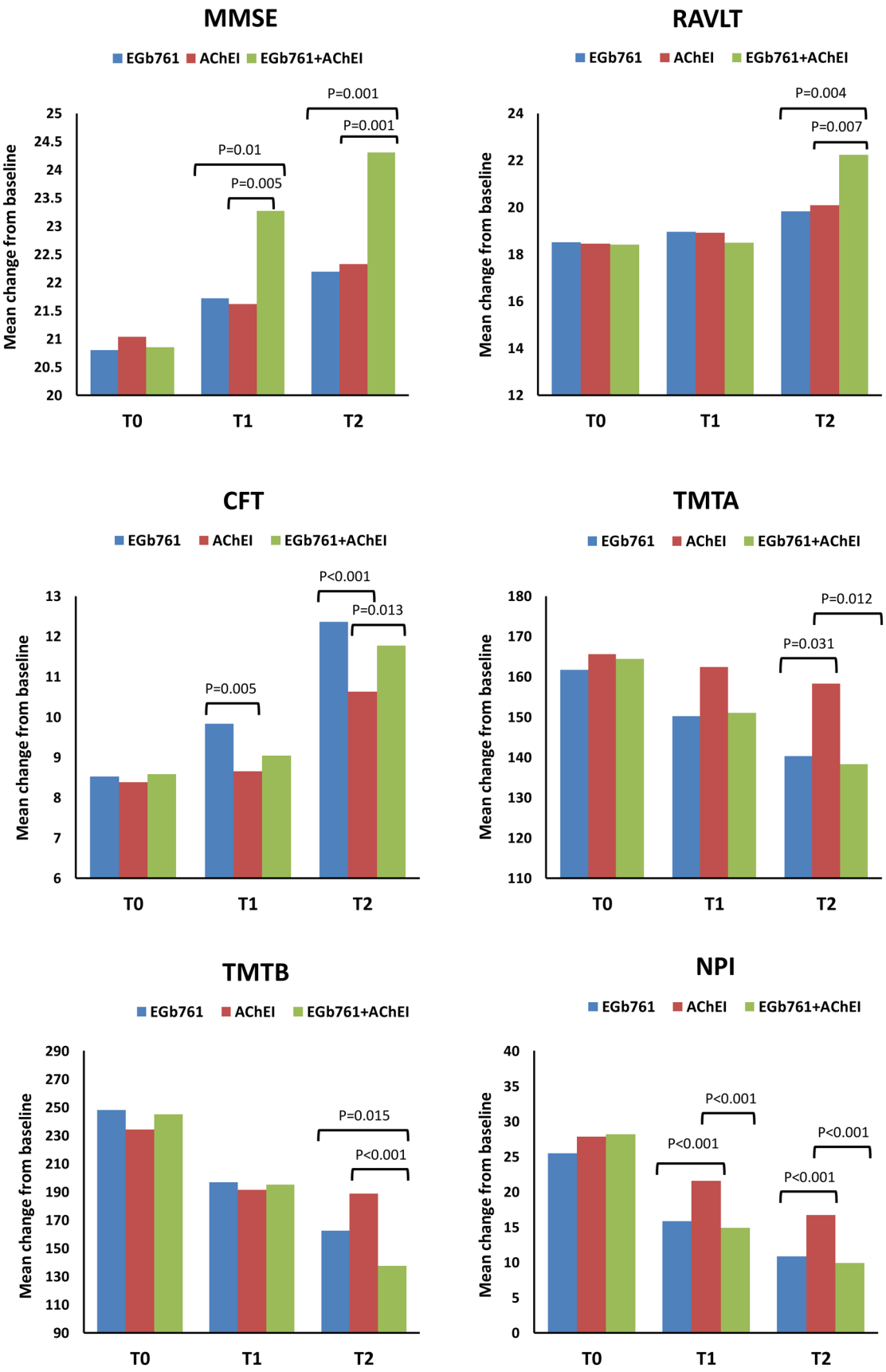
Variable	EGb 761 ($n=25$)	AChEI ($n=26$)	EGb 761+AChEI ($n=26$)	p-value ANCOVA
MMSE (T0)	20.80±2.22	21.04±1.91	20.85±2.57	0.922
MMSE (T1)	21.72±2.03	21.62±2.14	23.27±1.18	0.002
MMSE (T2)	22.20±2.10	22.31±2.31	24.31±1.32	<0.0001
RAVLT (T0)	18.52±2.89	18.46±3.29	18.42±2.76	0.993
RAVLT (T1)	18.96±2.75	18.92±3.04	18.50±2.53	0.805
RAVLT (T2)	19.88±2.45	20.00±2.86	22.23±2.89	0.002
CFT (T0)	8.52±0.92	8.38±0.75	8.58±1.14	0.756
CFT (T1)	9.84±1.79	8.65±0.89	9.04±0.99	0.005
CFT (T2)	12.36±1.49	10.62±1.17	11.77±1.53	<0.0001
LFT (T0)	8.76±1.05	8.77±1.03	8.88±1.24	0.905
LFT (T1)	9.68±1.21	9.85±1.29	10.12±1.53	0.513
LFT (T2)	11.44±1.58	10.96±1.37	11.88±1.79	0.120
TMTA (T0)	161.64±25.13	165.62±21.59	164.35±21.80	0.819
TMTA (T1)	150.20±24.80	162.42±24.73	151.08±22.11	0.130
TMTA (T2)	140.32±23.99	158.23±27.38	138.31±20.96	0.007
TMTB (T0)	248.00±29.35	234.15±30.49	245.08±26.27	0.201
TMTB (T1)	196.84±35.03	191.23±39.76	195.15±26.11	0.833
TMTB (T2)	162.52±32.01	183.77±41.09	137.27±14.01	<0.0001
SDMT (T0)	21.04±10.59	22.08±7.28	22.23±9.59	0.883
SDMT (T1)	28.28±9.83	28.15±8.36	23.42±10.40	0.122
SDMT (T2)	35.00±7.86	35.54±8.33	29.38±11.37	0.037
BNT (T0)	9.20±2.31	8.27±2.89	9.23±2.97	0.364
BNT (T1)	10.80±1.50	10.81±1.17	11.12±1.48	0.650
BNT (T2)	12.36±1.32	12.27±1.12	11.85±1.29	0.292
NPI (T0)	25.48±6.75	27.85±7.39	28.19±6.38	0.315
NPI (T1)	15.80±6.02	21.54±5.60	14.85±4.78	<0.0001
NPI (T2)	10.80±5.59	16.69±4.48	9.92±3.25	<0.0001
IDDD (T0)	48.44±10.94	52.81±13.32	51.50±10.81	0.402
IDDD (T1)	47.32±10.29	50.96±10.25	52.46±13.46	0.265
IDDD (T2)	49.20±11.88	55.00±14.02	51.50±10.16	0.234

Values are mean ± SD

T0 baseline, T1 follow-up 6 months, T2 follow-up 12 months;

ANCOVA analysis of covariance, *BNT* Boston Naming Test, *CFT* Category Fluency Test, χ^2 Chi-square, *IDDD* Interview for Deterioration in Daily Living Activities in Dementia, *LFT* Letter Fluency Test, *MMSE* Mini Mental State Examination, *NPI* Neuropsychiatric Inventory, *RAVLT* Rey Auditory Verbal Learning Test, *SDMT* Symbol Digit Modalities Test, *TMTA* Trail Making Test part A, *TMTB* Trail Making Test part B

previous studies have shown convincing results on the efficacy of using EGb 761 and sometimes even other Ginkgo extracts to improve cognitive function and neuropsychiatric symptoms in patients with VCI. In a randomized clinical trial, Ginkgo extract showed a statistically significant positive effect in comparison with placebo on the Clinical Global Impression score in combination with few adverse effects [48]. EGb 761 is also widely used in the treatment of acute ischemic stroke in some countries [49]. Recent studies found EGb 761 and other *Ginkgo biloba* extracts to be beneficial and safe in the treatment of acute cerebral infarction, improving the outcome and showing neuroprotective effects [50, 51]. The results of a recent systematic review and meta-analysis strengthens the evidence that EGb 761 has a beneficial therapeutic effect on patients with ischemic stroke [52]. These positive results could be related to the complex mechanism of action of EGb 761 with pharmacological effects that include antioxidant activities, increased tolerance to hypoxia, improvement of blood rheology by increasing the flexibility of the cellular components of the blood, thus improving microcirculation, and prevention of cerebral edema [31–35, 53]. More recently, the results of a systematic review and meta-analysis support the efficacy of EGb 761 for vascular cognitive impairment, and it appeared to be well tolerated. The main finding of this review was that EGb 761 treatment appears to be more effective than


MMSE
EGb761 AChEI EGb761+AChEI
Mean change from baseline
25
24.5
24
23.5
23
22.5
22
21.5
21
20.5
20
P=0.01
P=0.005
P=0.001
P=0.001
T0
T1
T2
RAVLT
EGb761 AChEI EGb761+AChEI
Mean change from baseline
24
22
20
18
16
14
12
P=0.004
P=0.007
T0
T1
T2
CFT
EGb761 AChEI EGb761+AChEI
Mean change from baseline
13
12
11
10
9
8
7
6
P=0.005
P<0.001
P=0.013
T0
T1
T2
TMTA
EGb761 AChEI EGb761+AChEI
Mean change from baseline
180
170
160
150
140
130
120
110
P=0.031
P=0.012
T0
T1
T2
TMTB
EGb761 AChEI EGb761+AChEI
Mean change from baseline
290
270
250
230
210
190
170
150
130
110
90
P=0.015
P<0.001
T0
T1
T2
NPI
EGb761 AChEI EGb761+AChEI
Mean change from baseline
40
35
30
25
20
15
10
5
0
P<0.001
P<0.001
P<0.001
P<0.001
T0
T1
T2

◂**Fig. 1** Mean cognitive and behavioral changes between-treatment groups as estimated by ANCOVA. T0 baseline, T1 follow-up 6 months, T2 follow-up 12 months. *CFT* Category Fluency Test, *MMSE* Mini Mental State Examination, *NPI* Neuropsychiatric Inventory, *RAVLT* Rey Auditory Verbal Learning Test, *TMTA* Trail Making Test part A, *TMTB* Trail Making Test part B

controls as assessed by various measures of cognitive function [54].

Cholinergic transmission deficits have been studied in VaD. Animal and human studies indicate that, as with AD, deficits in cholinergic transmission may be responsible for the development of cognitive impairment associated with VaD [55].

In this sense, it has been suggested that patients with VaD also exhibit cholinergic deficits [56]. Postmortem examinations have revealed significant reductions in choline acetyltransferase activity in the hippocampus and temporal cortex of VaD patients [57]. Tohgi et al [58] and Wallin et al [59] observed significantly reduced CSF choline acetyltransferase concentrations in patients with Binswanger or multi-infarct dementia. Other studies confirmed the association of cholinergic pathways with dementia severity in subcortical vascular cognitive impairment [60].

These results suggest a rational basis for cholinergic therapy in VaD based on the ability of AChEI to increase the concentration of neurotransmitter in the brain and improve memory [61–63]. A recent Cochrane Collaboration systematic review found moderate-to-high certainty evidence that donepezil 5 mg, donepezil 10 mg, and galantamine have a slight beneficial effect on cognition in people with VCI, although the size of the change is unlikely to be clinically important. Donepezil 10 mg and galantamine 16 to 24 mg are associated with more adverse events than placebo. The evidence for rivastigmine was less certain. The effect of AChEI for VaD is modest, but in the absence of any other treatments, people living with VCI may still wish to consider the use of these agents [22].

More specifically, the combination of the two drugs was associated with an improvement in MMSE scores at both 6 and 12 months compared to the AChEI alone group and EGb 761 alone, RAVLT at 12 months compared to AChEI alone group and EGb 761 alone, CFT at 12 months compared to AChEI alone, TMTA at 12 months compared to the AChEI alone group, TMTB at 12 months compared to the AChEI alone group and EGb 761 alone, and NPI at both 6 and 12 months compared to the AChEI alone group.

The precise mechanism of action that explains these results is not yet known, but a possible synergistic effect cannot be ruled out. Several investigations have shown a cholinergic deficit in subjects with VaD related to reduced acetylcholinesterase activity [55, 61–63]. In this sense, the beneficial effect of AChEIs is based on the characteristic of inhibiting acetylcholinesterase enzyme activity with the potential restoration of physiological acetylcholine levels at the synapse. Thus, the enhanced postsynaptic activity promotes a more normal function of the cholinergic system [55, 61–63]. This is important in the medial temporal lobe and especially the hippocampus because both play a crucial role in memory [64, 65]. On the other hand, the presence of vascular pathology causes arterial stiffness and modifies the structure of cerebral blood vessels and alters the delicate vasoregulatory mechanisms that ensure an adequate blood supply to the brain. These alterations put at risk the adequate supply of cerebral blood and increase the vulnerability of the brain to ischemic injury as well as VCI [66, 67].

Overall, the benefit observed in our study with the combined treatment with EGb 761 and AChEIs could be explained by the possible addition of the acetylcholinesterase inhibitory effect exerted by AChEIs together with the potential effects of EGb 761 protecting against ischemia, generation of free radicals and reactive oxygen species, improving microcirculation and exerting a neuroprotective effect [35, 53, 68, 69].

A strength of this study was the long duration of the follow-up, which suggests that the clinical benefit of EGb 761+AChEIs may be greater after long-term use. In addition, patients in the study underwent a comprehensive neuropsychological, behavioral, and functional evaluation with widely used outcome measures focused on reducing observation bias. In addition, our semi-annual evaluations, allowed close monitoring of clinical changes. However, given that this was a retrospective study, and the participating subjects were not randomly assigned to treatment groups, the results obtained could be affected by this circumstance. Moreover, the observational design did not allow us to conclude on causality. On the other hand, we analyzed the AChEIs as a whole without specifying any of them in particular. It is therefore possible that clinical differences may exist if the different AChEIs were studied individually. In this sense, results from Battle et al [22] found moderate-to high certainty evidence that donepezil 5 mg, donepezil 10 mg, and galantamine have a slight beneficial effect on cognition in people with vascular cognitive impairment, although the size of the change is unlikely to be clinically important. The evidence for rivastigmine was less certain.

5 Conclusions

Vascular pathology has a central role in cognitive deterioration. The *Ginkgo biloba* extract EGb 761 showed cognitive and behavioral benefits in patients suffering from VaD. These positive effects increased when EGb 761 and AChEIs were used in combined treatment, probably providing additional benefits by targeting different pathophysiological

Table 4 Treatment-related adverse events reported%

	EGB 761 ($n=25$)	AChEI ($n=26$)	EGb 761+AChEI ($n=26$)	p-value Fisher's exact test
Nausea	2 (8%)	7 (27%)	4 (13.40%)	0.45
Headache	2 (8%)	5 (19.23%)	3 (11.54%)	0.23
Dizziness	1 (4%)	6 (23.07%)	6 (23.07%)	0.55
Constipation	1 (4%)	3 (11.54%)	3 (11.54%)	0.12
Diarrhea	1 (4%)	6 (23.07%)	4 (13.40%)	0.55
Insomnia	3 (12%)	4 (13.40%)	3 (11.54%)	0.10
Somnolence	1 (4%)	3 (11.54%)	2 (7.70%)	0.76
Tremor	0	1 (3.84%)	0	0.31
Aggressiveness	0	1 (3.84%)	0	0.89
Fatigue	1 (4%)	5 (19.23%)	2 (7.70%)	0.73
Abdominal pain	0	2 (7.70%)	0	0.44
Vertigo	0	4 (13.40%)	2 (7.70%)	0.66
Agitation	0	3 (11.54%)	1 (3.84%)	0.46
Skin rashes	0	6 (23.07%)	5 (19.23%)	0.05
Dry mouth	0	2 (7.70%)	2 (7.70%)	0.36

mechanisms. Thus, these findings provide clinicians with new insight into the pharmacological management of VaD. This study can serve as a model for the design of future long-term randomized controlled trials that help to support the combined use of EGb 761 and cholinesterase inhibitors in VaD patients.

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Declarations

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Conflict of interest The authors declare that there is no conflict of interest.

Ethics Approval All procedures in this study were in accordance with the 1964 Helsinki declaration (and its amendments). The study was approved by the ethics committee of the Instituto Andaluz de Neurociencia.

Consent to participate All patients or their representative caregivers signed an informed consent form.

Consent for publication Not applicable.

Availability of data and material The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Authors' contributions JMG-A designed the study; JMG-A, SM and EG collected the study data; JMG-A performed statistical analysis and wrote the manuscript.

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