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Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study

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The Ginkgo biloba special extract EGb 761 seems to produce neuroprotective effects in neurodegenerative diseases of multifactorial origin. There is still debate about the efficacy of Ginkgo biloba special extract EGb 761 compared with second-generation cholinesterase inhibitors in the treatment of mild to moderate Alzheimer's dementia. Our aim is to assess the efficacy of the Ginkgo biloba special extract E.S. in patients with dementia of the Alzheimer type in slowing down the disease's degenerative progression and the patients' cognitive impairment compared with donepezil and placebo. The trial was designed as a 24-week randomized, placebo-controlled, double-blind study. Patients aged 50–80 years, suffering from mild to moderate dementia, were allocated into one of the three treatments: Ginkgo biloba (160 mg daily dose), donepezil (5 mg daily dose), or placebo group. The degree of severity of dementia was assessed by the Syndrom Kurz test and the Mini-Mental State Examination. Clinical Global Impression score was recorded to assess the change in the patients' conditions and the therapeutic efficacy of tested medications. Our results confirm the clinical efficacy of Ginkgo biloba E.S. (Flavogin) in the dementia of the Alzheimer type, comparable with donepezil clinical efficacy. There are few published trials that have directly compared a cholinesterase inhibitor with Ginkgo for dementia. This study directly compares a cholinesterase inhibitor with Ginkgo biloba for dementia of the Alzheimer type and could be a valid contribution in this debate. Our study suggests that there is no evidence of relevant differences in the efficacy of EGb 761 and donepezil in the treatment of mild to moderate Alzheimer's dementia, so the use of both substances can be justified. In addition, this study contributes to establish the efficacy and tolerability of the Ginkgo biloba special extract E.S. in the dementia of the Alzheimer type with special respect to moderately severe stages.

Introduction

The Ginkgo biloba special extract EGb 761 seems to produce neuroprotective effects in neurodegenerative diseases of multifactorial origin [1]. EGb 761 has been licensed for many years and has been investigated in various clinical studies with different target variables. In particular, substantial evidence suggests that EGb 761 protects hippocampal neurons against cell death induced by β-amyloid [2]. Evidences for the pharmacological actions of Ginkgo biloba extract stem from clinical studies in humans, pharmacological trials in animals and *in vitro* studies. The main effects of Ginkgo biloba extract in the central nervous system seem to be related to its antioxidant properties, which require the synergistic action of the flavonoids, the terpenoids (ginkgolides, bilobalide), and the organic acids. These compounds to varying degrees act as scavengers for free radicals, which have been considered the mediators of the excessive lipid peroxidation and cell damage observed in Alzheimer's disease [3]. In brief, several mechanisms of action have been described to explain the nootropic properties of Ginkgo biloba: increased tolerance to hypoxia; improvement of blood rheology and vasoregulating capacity, resulting in increased blood flow; prevention of post-traumatic or toxin-induced brain edema; platelet activating factor inhibition; neuroprotective action by direct or by indirect influences on the nervous system [4].

Some clinical trials in the last years showed how Ginkgo could be effective as a treatment for older people with mild to moderate dementia, considering that there were significant differences in response rates between active substance and placebo. Therefore, there is still debate about the efficacy of Ginkgo biloba special extract EGb 761 compared with second-generation cholinesterase inhibitors (donepezil, rivastigmine, metrifonate) in the treatment of mild to moderate Alzheimer's dementia [4,5].

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The aim of this study was to assess the efficacy of the Ginkgo biloba special extract E.S. in patients with dementia of the Alzheimer type in slowing down the disease's degenerative progression and the patient's cognitive impairment.

Methods

The trial was designed as a randomized, placebo-controlled, double-blind study. Patients aged 50–80 years, suffering from mild to moderate dementia, were allocated into one of the three treatments: Ginkgo biloba (160 mg daily dose), donepezil (5 mg daily dose), or placebo group. All participants received a diagnosis of primary degenerative dementia of the Alzheimer type according to the criteria of DSM-IV [6]. Inclusion criteria were: (i) a mean score of 3–5 on the *Brief Cognitive Rating Scale* [7], a *Hachinski Ischemic Score* [8] of < 4 and the presence of an adequate level of premorbid intelligence (IQ $>$ 80, global assessment).

Patients were excluded if they had dementia of other etiology, severe organic diseases (tumors, severe infectious diseases, brain trauma, epilepsy, cerebrovascular malformations, alcohol or drug abuse), pseudodementia or a history of schizophrenic or affective psychoses (Geriatric Depression Scale, 15-item version, total score < 11) [9].

The degree of severity of dementia had to be mild to moderate as assessed by a score between 8 and 23 on the Syndrom Kurz test (SKT) [10], a psychometric test battery for the assessment of memory and attention. The SKT consists of nine 1-min subtests that are partly speed-oriented and partly span-oriented: scaled subtest scores are aggregated to an SKT total status score ranging from 1 (very good) to 27 (very poor). Clinical Global Impression (CGI) score was recorded at baseline and at monthly intervals to assess the change in the patients' condition and the therapeutic efficacy of tested medications. In particular, psychopathology over time was assessed by the CGI item 2 (CGI-2): this rating instrument expresses the global change in observable cognitive functioning directly on a transitional scale ranging from 1 (very much improved) to 7 (very much deteriorated) [4]. Another baseline and outcome measure was Mini-Mental State Examination (MMSE): subjects who reached a score of at least 13 but no more than 25 on the MMSE were considered for study participation.

For randomization procedure we used a computer-generated random sample set. From March 2003 to March 2004, 150 outpatients were screened for dementia according to the above criteria; 117 patients were enrolled in the study, 41 were excluded and 76 were randomly allocated (1:1:1). A trial design is shown in Fig. 1. Laboratory tests and computed tomographic scans were performed routinely. A single-blind placebo 4-week run-in period was included to exclude placebo-responders. Demographic and baseline characteristics are shown in Table 1. The duration of the study was 24 weeks. The subjects were informed about the procedures and aims of the study, its characteristics, and possible side effects of the drug and gave their approval through informed consent. The study was approved by the local ethics committee.

The researchers who provided the pills to the study participants were different from those who conducted the neuropsychological evaluations, in order to guarantee the blinding.

Vasoactive drugs, nootropics and long-term treatment with other drugs were proscribed during the study, with the exception of low doses of benzodiazepines and neuroleptics in the treatment of behavioral disturbances.

Statistical analysis

Statistical analysis was performed with SPSS software (v.12.0; SPSS Inc., Chicago, IL, USA); *t*-test for paired samples was used to compare each group from baseline to 24 weeks of treatment. An analysis of variance (ANOVA) was performed to detect difference between groups. Age, gender, and severity of cognitive impairment at baseline were factors of ANOVA model. All data are showed as mean $\pm$ standard deviation (SD), interval of confidence was at 95%.

Results

At the end of the study, after 24 weeks of treatment period, 60 patients completed the trial. Of 76 subjects randomized for the study, 15 withdrawn: five patients in the EGb group (20%), four patients in donepezil group (16%), and six in placebo group (23%). Causes of drop-out are shown in Fig. 2. In particular, in the treatment group (EGb and donepezil) the major cause of withdrawal was lost at follow-up and in one case in Ginkgo group was a caregiver request. In placebo group loss of efficacy was the first cause for withdrawal.

Outcome measures

All data are resumed in Table 2. Data are showed as result of an intent-to-treat analysis. All values are expressed as mean change from baseline with CI at 95%, considering the end of 24 weeks of treatment as the final time end-point. Regarding MMSE, we observed an improvement of MMSE scores in the EGb and donepezil groups and a slight worsening in placebo

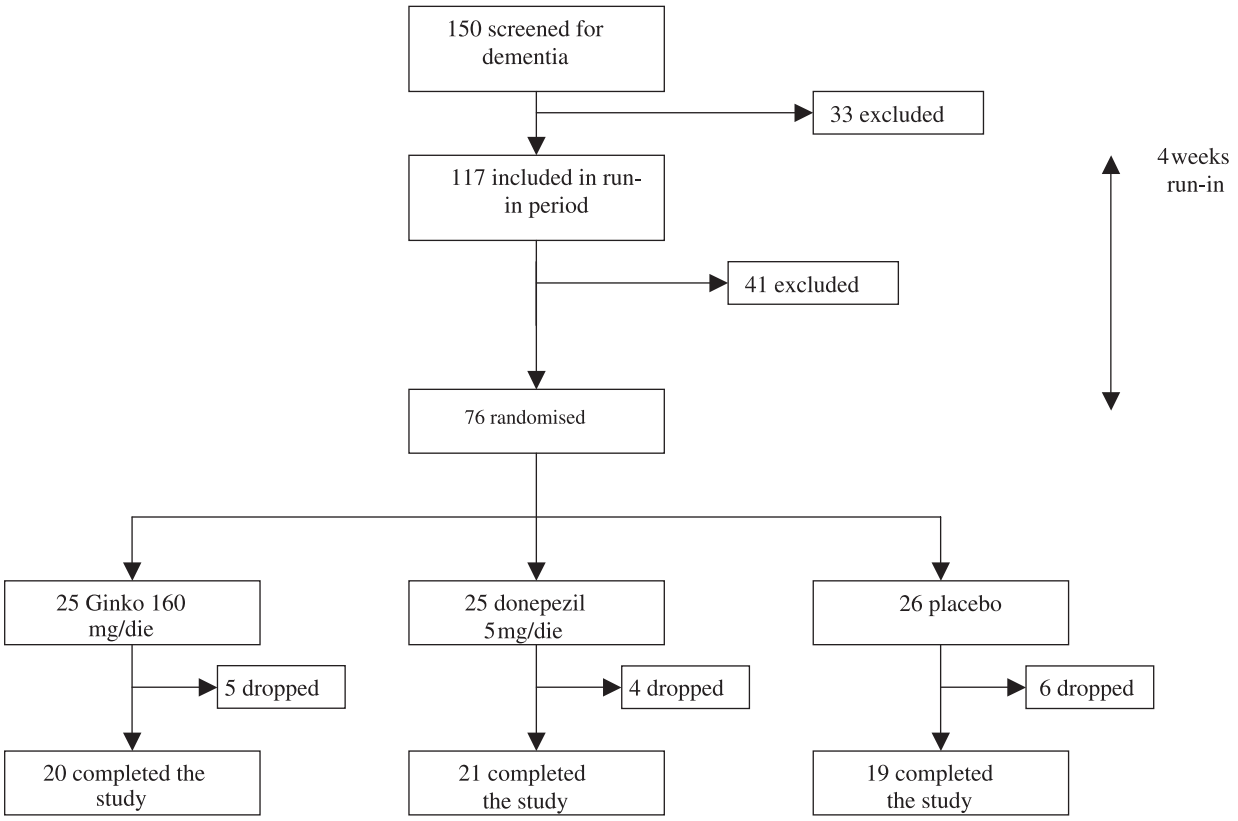

Figure 1 Design of the study.

Table 1 Demographic and baseline characteristics of patients included in the study

	All	EGb	Donepezil	Placebo
Number of patients	76	25	25	26
Male	35 (46)	12 (48)	13 (52)	10 (39)
Female	41 (54)	13 (52)	12 (48)	16 (61)
Age (years)	68.5 ± 5	66.2 ± 6	64.5 ± 6	69.8 ± 3
MMSE	18.71 ± 3.51	18.80 ± 3.62	18.55 ± 3.47	18.80 ± 3.63
SKT	14.73 ± 3.46	16.45 ± 3.05	15.15 ± 3.48	15.9 ± 3.86
CGI (item 2)	4.73 ± 0.89	4.65 ± 0.87	4.5 ± 0.76	5.05 ± 0.99

Values represent mean ± standard deviation and number (%) of patients.

group: mean value was from 18.80 ± 3.622 (SD) at baseline to 19.40 ± 3.485 (SD) at 24 weeks period for EGb group, from 18.55 ± 3.47 (SD) to 19.75 ± 3.160 (SD) for donepezil, and from 18.80 ± 3.636 (SD) to 18.55 ± 3.663 (SD) for placebo. No significant change was observed for each group (*t*-test analysis and 95% CI), and ANOVA for treatment difference shows no significance for both EGb group and donepezil group (Fig. 2).

As regard SKT we observed an improvement of SKT scores in the EGb and donepezil group: mean values passed from 15.90 ± 3.86 (SD) at baseline to 16.90 ± 3.9 (SD) at 24 weeks for placebo; from 16.45 ± 3.05 (SD) to 13.15 ± 2.9 (SD) for EGb group, from 15.15 ± 3.48(SD) to 11.85 ± 2.9 (SD) for donepezil. A statistical significance was observed for EGb and donepezil group in a *t*-test comparison, both groups show also a significant difference when compared with placebo group in an ANOVA. Placebo group shows a statistically significant worsening ($P = 0.01$). No difference was found in comparison between donepezil and EGb. Data are disposed in Fig. 3.

There was a significant difference in CGI scores changes for donepezil and EGb group from baseline to the end of 24 weeks of treatment. Mean values passed from 5.05 ± 0.99 (SD) at baseline to 5.2 ± 0.95 (SD) at 24 weeks for placebo; from 4.65 ± 0.87 (SD) to 3.75 ± 0.96 (SD) for EGb group, from 4.5 ± 0.76 (SD) to 3.6 ± 0.94 (SD) for donepezil. These data are also confirmed when both groups are compared with placebo. No difference was found between donepezil and EGb groups (Fig. 4).

Discussion and conclusions

Our randomized placebo-controlled double-blind study compared the efficacy and tolerability of the EGb 761 to donepezil in the treatment of mild to moderate

Figure 2 MMSE scores at baseline and after 24 weeks.

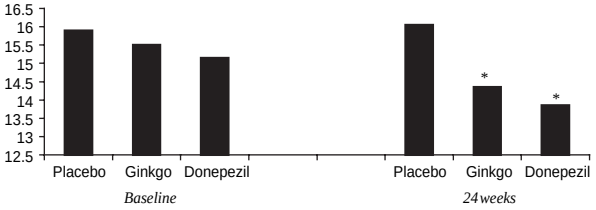

Figure 3 SKT scores at baseline and after 24 weeks. Ginkgo and donepezil groups show a statistically significant difference compared with placebo (*$P = 0.01$).

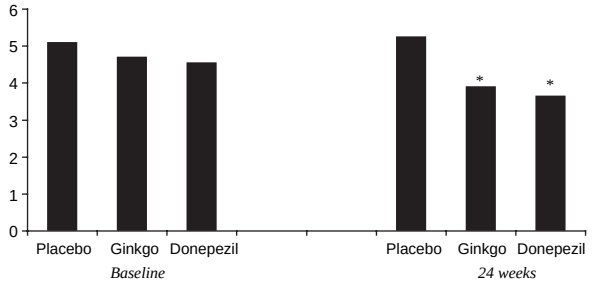

Figure 4 CGI scores at baseline and after 24 weeks. Ginkgo and donepezil groups show a statistically significant difference compared with placebo (*$P = 0.01$).

Alzheimer's dementia. One of the most important parameters in demonstrating the clinical efficacy of an antidementia drug is the improvement in cognitive performance. MMSE, SKT, and CGI are some of the most common instruments used in clinical evaluation of cognitive impairment. Our results confirm the clinical efficacy of Ginkgo biloba E.S. in the dementia of the Alzheimer type, comparable with donepezil clinical efficacy. The SKT has been largely used by other studies and has proved useful for this purpose [11,12]. Compared with the donepezil-treated group, the patients' attention, memory and cognitive performance after 6 months of treatment as measured by the SKT test had shown a comparable important improvement. Therefore, the effectiveness of Ginkgo biloba E.S. can be confirmed by considering the significant group differences in SKT score changes from the baseline to the final results.

We can also notice a significant improvement in CGI scores after 6 months in patients treated with Ginkgo biloba E.S., comparable with the improvement obtained by the donepezil sample. These data contribute to stress the efficacy of the Ginkgo biloba E.S. in changing the patients' condition during treatment.

It is important to underline that the effect of Ginkgo biloba special extract was large enough to reach clinical significance, even with such relatively small samples of patients. Our results agree with those showed by previous studies in the literature in which identical or similar geriatric scales were used and evaluated. Concrete evidence of the efficacy of Ginkgo biloba E.S. can be clearly seen by considering the change in the patient's clinical conditions during treatment: for example, the patients' attention and memory performance after 6 months of treatment as measured by the SKT had shown significant improvement, comparable with the results obtained by patients treated with donepezil.

There were five (20%) drop-outs in the Ginkgo biloba group and four (16%) drop-outs in the donepezil group. Considering the limited sample evaluated, Ginkgo biloba group shows a small dropout rate, which indicates that it has a good side effect profile. The drop-outs in the donepezil group were due to adverse events

Table 2 Outcome measures: intent to treat analysis*

	Mean change from baseline (95% CI)		
Group	MMSE	SKT	CGI (item 2)
Placebo	−0.25 (−2.17 to 2.67)	0.9 (−1.3 to −0.4), $P = 0.01$	0.15 (−0.3 to 0.02)
EGb group	0.6 (−3 to 1.8)	−3.3 (2.3 to 4.27)*, $P < 0.001$	−0.9 (0.5 to1.2)*, $P < 0.001$
Donepezil group	1.2 (− 3.6 to 1.2)	−3.3 (2.3 to 4.29)*, $P < 0.001$	−0.9 (0.5 to1.2)*, $P < 0.001$
Treatment difference for EGb group	−0.85 (−3.27 to 1.5), $P = 0.1$ (ns)	− 3.65 (1.04 to 6.2)*, $P < 0.001$	−1.35 (0.6 to 2.0)*, $P < 0.001$
Treatment difference for donepezil group	−1.2 (−3.6 to 1.2), $P = 0.06$ (ns)	− 5.7 (2.3–7.5)*, $P < 0.001$	−1.6 (0.9 to 2.2)*, $P < 0.001$

*Significance at 95% CI. MMSE, Mini Mental State Examination; SKT, Syndrom Kurz test; CGI (item 2), Clinical Global Impression. No statistical significance for donepezil versus EGb (data not shown).

Table 3 Drop-out: number (%) of patients

	EGb	Donepezil	Placebo
Total	5/25 (20)	4/25 (16)	6/26 (23)
Loss of efficacy	0	0	4 (15.4)
Loss of follow-up	3 (12)	0	2 (7.6)
Caregiver request	2 (8)	0	0
Adverse event	0	4 (16)	0

(diarrhea, nausea, vomiting and restlessness), the same observed in other studies [13]. On the contrary, the drop-outs in the Ginkgo biloba group were not imputable to adverse events, so that the Ginkgo biloba E.S. has demonstrated a confirmed good tolerability (Table 3).

A recent study [14] reported that 6 weeks of treatment with Ginkgo biloba failed to improve performance on standardized neuropsychological tests of learning, memory, attention and verbal ability in healthy elderly adults without cognitive impairment. We agree with Nathan [15, 16] in suggesting that Ginkgo's effects may be explained by its modulatory influence on the human cholinergic system. The mechanisms of action are thought to reflect the synergistic action of several components of the extract and include increasing blood supply by dilating blood vessels, reducing blood viscosity, modification of neurotransmitter systems, and reducing the density of oxygen-free radicals.

There are few published trials that have directly compared a cholinesterase inhibitor with Ginkgo for dementia. This study directly compares a cholinesterase inhibitor with Ginkgo biloba for dementia of the Alzheimer type and could be a valid contribution in this debate.

Nowadays the costs of the drugs used for Alzheimer disease are very high, especially if compared with the clinical benefits. In such perspective it results useful to look for cheaper, effective and well-tolerated alternative drugs such as Ginkgo biloba.

Larger samples of patients should be considered indeed to confirm these results. Our study suggests that there is no evidence of relevant differences in the efficacy of EGb 761 and donepezil in the treatment of mild to moderate Alzheimer's dementia, so the use of both substances can be justified. In addition, this study contributes to establish the efficacy and tolerability of the Ginkgo biloba special extract E.S. in the dementia of the Alzheimer type with special respect to moderately severe stages.

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