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A Placebo-Controlled, Double-blind, Randomized Trial of an Extract of Ginkgo Biloba for Dementia

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Context. – EGb 761 is a particular extract of Ginkgo biloba used in Europe to alleviate symptoms associated with numerous cognitive disorders. Its use in dementias is based on positive results from only a few controlled clinical trials, most of which did not include standard assessments of cognition and behavior.
Objective. – To assess the efficacy and safety of EGb in Alzheimer disease and multi-infarct dementia.
Design. – A 52-week, randomized double-blind, placebo-controlled, parallelgroup, multicenter study.
Patients. – Mildly to severely demented outpatients with Alzheimer disease or multi-infarct dementia, without other significant medical conditions.
Inervention. – Patients assigned randomly to treatment with EGb (120 mg/d) or placebo. Safety, compliance, and drug dispensation were monitored every 3 months with complete outcome evaluation at 12, 26, and 52 weeks.
Primary Outcome Measures. – Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Geriatric Evaluation by Relative's Rating Instrument (GERRI), and Clinical Global Impression of Change (CGIC).
Results. – From 309 patients included in an intent-to-treat analysis, 202 provided evaluable data for the 52-week end point analysis. In the intent-to-treat analysis, the EGb group had an ADAS-Cog score 1.4 points better than the placebo group (P=.04) and a GERRI score 0.14 points better than the placebo group (P=.004). The same patterns were observed with the evaluable data set in which 27% of patients treated with EGb achieved at least a 4-point improvement on the ADAS-Cog, compared with 14% taking placebo (P=.005); on the GERRI, 37% were considered improved with EGb, compared with 23% taking placebo (P=.003). No difference was seen in the CGIC. Regarding the safety profile of EGb, no significant differences compared with placebo were observed in the number of patients reporting adverse events or in the incidence and severity of these events.
Conclusion. – EGb was safe and appears capable of stabilizing and, in a substantial number of cases, improving the cognitive performance and the social functioning of demented patients for 6 months to 1 year. Although modest, the changes induced by EGb were objectively measured by the ADAS-Cog and were of sufficient magnitude to be recognized by the caregivers in the GERRI.

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THE EXTRACT of Ginkgo biloba referred to as EGb 761 is one of the most popular plant extracts[1] used in Europe to alleviate symptoms associated with a range of cognitive disorders.[2] It has recently been approved in Germany for the treatment of dementia. The mechanism of action of EGb in the central nervous system is only partially understood, but the main effects seem to be related to its antioxidant properties, which require the synergistic action of the flavonoids, the terpenoids (ginkgolides, bilobalide), and the organic acids, principal constituents of EGb.[3] These compounds to varying degrees act as scavengers for free radicals,[2,4] which have been considered the mediators of the excessive lipid peroxidation and cell damage observed in Alzheimer disease (AD).[5-8] Although several European studies[9-13] report positive results of EGb 761 in the treatment of diverse neurological disorders, few studies using standard methods have evaluated the cognitive and behavioral effects of EGb in dementia.[13] Further, no empirical clinical trials of the extract have been conducted in the United States. Therefore, this multicenter placebo-controlled study was undertaken to assess the efficacy and safety of EGb in AD and multi-infarct dementia (MID).

METHODS

Patient Population

Patients of both sexes, 45 years of age or older, with a diagnosis of uncomplicated dementia according to *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R)* and *International Statistical Classification of Diseases, 10th Revision (ICD-10)* criteria, either Alzheimer type (AD) or MID, were enrolled in the study. The severity of the dementia at screening was mild to moderately severe as assessed by a Mini-Mental State Examination[14] score of 9 to 26 (inclusive) and a Global Deterioration Scale score[15] of 3 to 6 (inclusive). To be eligible, patients had to have no other significant medical conditions including cardiac disease, insulindependent diabetes, liver disease, chronic renal insufficiency, or another psychiatric disorder as a primary diagnosis. Patients with brain mass or intracranial hemorrhage determined by computed tomography or magnetic resonance imaging were excluded.

The use of medications for preexisting conditions was not discontinued at screening, but change in regimen or prescription of new concomitant medications known to affect cognitive function was not permitted during the study. Noncompliance was monitored by pill counts and defined by a deviation of more than 20% from the study regimen.

The study protocol and the informed consent forms were approved by the institutional review boards of the Massachusetts Mental Health Center of Harvard Medical School, Boston, and New York Institute for Medical Research, Tarrytown. Written informed consent was obtained from the patients or their legal representatives and from the caregivers.

Study Design

The study used a 52-week, double-blind, fixed-dose, placebo-controlled, parallel-group randomized design and was conducted at 6 research centers in the United States. Patients underwent a 14-day single-blind placebo run-in period. Safety assessments (adverse events and vital signs), pill counts, and drug dispensation were performed at 4-, 12-, 26-, 39-, and 52-week visits. Complete assessments of primary outcome measures were required at baseline and at 12, 26, and 52 weeks. At screening and at termination, extensive medical, neurological, and psychiatric evaluations were performed, including electroencephalogram and laboratory tests (blood cell count, routine chemistry, vitamin B_{12}, folate, triiodothyronine, thyroxine, and thyrotropin). National Health Laboratories, Cranford, NJ, was used as a central laboratory to collect and analyze all laboratory work from each site. All randomization procedures, drug packaging, storage of codes and other study materials, and study monitoring were managed by International Drug Development Corporation, Parsippany, NJ. EGb (Murdock, Springville, Utah) was supplied as a 40-mg tablet to be swallowed before each of the 3 principal daily meals, for a total daily dose of 120 mg. Patients were consecutively assigned to EGb or to placebo following a predetermined order based on separate randomization schedules for each center using balanced blocks of 10 patients. Consecutive numbers were printed on each drug study pack, and randomization codes, stored in sealed envelopes,

were exclusively retained by International Drug Development Corporation independently from sponsor and investigating centers.

The EGb and the matched placebo tablets did not differ in their appearance and were film coated to ensure a similar smell and taste. EGb had the identical formulation and chemical composition as the product used in Germany (Tebonin forte, Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe). The study drugs were made by a standard method and came from the same batch of Ginkgo extract. EGb is a standardized concentrated extract from the dried leaves of the Ginkgo biloba tree, specially produced by means of a multiplestep extraction procedure and consisting of 24% Ginkgo-flavoneglycosides and 6% terpenelactones (3.1% ginkgolides A, B, and C, 2.9% bilobalide).

Outcome Measures

The primary outcome measures assessed changes in 3 areas: (1) *Cognitive impairment* was assessed by the cognitive subscale of the Alzheimer's Disease Assessment Scale[16, 17] (ADAS-Cog), a performance-based cognitive test that objectively evaluates memory, language, praxis, and orientation. The test includes 11 items with a total score ranging from 0 to 70; the higher the score, the poorer the performance. (2) *Daily living and social behavior* was assessed by the total score of the Geriatric Evaluation by Relative's Rating Instrument[18] (GERRI), a 49-item rating inventory completed by the caregiver. The total score is the grand mean of the following 3 subscale means: the GERRI-cognitive (21 items), the GERRI-social (18 items), and the GERRI-mood (10 items). The scores of each item, thus, of each subscale and of the grand mean, range from 1 to 5; the higher the score, the poorer the patient's functioning in the home environment. The questions are presented in an identical checklist at each visit and are answered by the caregiver who evaluates the patient's functioning during the 14 days prior to the assessment. The GERRI total score was found to be highly correlated with the overall symptom severity of the dementia, as assessed by the Global Deterioration Scale.[18] However, longitudinal studies of annual GERRI change scores are few[19] and its validity in this respect has yet to be rigorously tested. (3) *General psychopathology,* the changes in overall psychopathology, was assessed by the Clinical Global Impression of Change[20] (CGIC), an interview-based global rating that quantifies the clinician's judgement of the amount of change in overall impairment compared with that at the study baseline. The CGIC does not follow a structured interview and uses a 7-point ordinal scale in which 1 is an extreme score indicating that the patient improved very much, and 7 indicates extreme worsening. Secondary outcomes of the study will be presented elsewhere.

Each subject was to complete 52 weeks, but if at any time a subject showed worsening of functioning or impairment, as assessed by an increase of 1 point on the CGIC, the subject could be dropped from the study and offered admission to an uncontrolled open-label humanitarian protocol. However, the investigator was encouraged to maintain the patient in the double-blind phase for at least 6 months. The confirmatory analysis was planned on "per protocol" valid cases with missing data at the 52-week end point visit replaced by last evaluable assessments after a minimum of 20 weeks of treatment (missing data at baseline were not replaced). An analysis of efficacy on an intent-to-treat (ITT) basis[21] with last observation carried forward was formulated as a secondary analysis. However, considering the relatively low proportion of patients completing the entire study and their unequal distribution between treatment arms, the ITT analysis was selected a posteriori as the primary analysis for efficacy.

Statistical Methods

It was planned to enroll 300 patients in the study. Owing to the higher prevalence of AD compared with MID,[22, 23] 70% of the total study patients were expected to have AD. However, there was no monitoring of the enrollment to control this ratio at the participating centers. The total sample size was calculated to detect a standardized treatment difference of 0.40 with a power of 80% (2-sample *t*-test, $\alpha = .05$, 2 sided), taking into account a predicted dropout rate of 20% during the entire course of the study. Data quality control and case classification for evaluable and ITT analyses were completed before breaking the double blind.

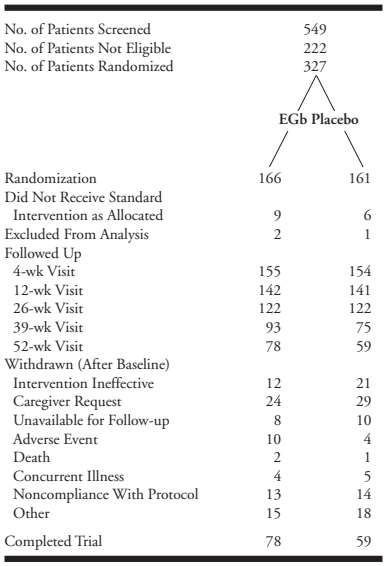

Figure 1. - Profile of the randomized controlled trial. Three patients were excluded from analysis because of protocol violations (2 because of diabetes mellitus and 1 because of unstable affective mood disorder).

Table 1. – Patient Characteristics at Baseline: Intent-to-Treat Analysis*

	All Diagnostic Groups			Alzheimer Disease		
	All	EGb Group	Placebo Group	All	EGb Group	Placebo Group
No. of subject	309	155	154	236	120	116
No. (%) of females	166 (54)	79 (51)	87 (56)	137 (58)	65 (54)	72 (62)
Age, *y*	69 (10)	69 (10)	69 (10)	68 (10)	68 (10)	68 (11)
Range	45-90	47-89	45-90	45-90	47-89	45-90
Median education, *y* (range)	14 (0-20)	14 (1-20)	14 (0-20)	14 (0-20)	14 (1-20)	14 (0-20)
Mini-Mental State Examination score	21.1 (5.6)	21.1 (5.8)	21.2 (5.5)	21.2 (5.7)	21.1 (5.9)	21.3 (5.6)
Range	6-30	8-28	6-30	6-30	8-28	6-30
ADAS-Cog score	20.2 (15.4)	20.0 (16.0)	20.5 (14.7)	20.2 (15.8)	19.7 (16.4)	20.2 (15.2)
Range	2-64	2-64	2-63	2-64	2-64	2-63
Disease duration, *y*	4.2 (3.7)	4.6 (4.3)	3.9 (3.0)	4.3 (3.8)	4.6 (4.4)	4.0 (3.2)
Range	0-36	0-36	0-20	0-36	0-36	0-20

* Data are given as mean (SD), unless otherwise specified. ADAS-Cog indicates Alzheimer's Disease Assessment Scale-Cognitive subscale.

Table 2. – Primary Outcome Measure Results: Intent-to-Treat Analysis*

	Mean Change From Baseline (95% CI) [n]		CGIC Rating Mean (95% CI) [n]
	ADAS-Cog	GERRI	
All diagnostic groups (N=309)			
EGb group	0.1 (-0.8 to 1.0) [136]	-0.06 (-0.13 to 0.01) [138]	4.2 (4.1 to 4.4) [155]
Placebo group	1.5 (0.4 to 2.5) [138]	0.08 (0.01 to 0.14) [132]	4.2 (4.1 to 4.3) [154]
Treatment difference	-1.4 (-2.7 to -0.0)	-0.14 (-0.23 to -0.04)	0.0 (-0.1 to 0.2)
P	.04	.004	.77
Alzheimer disease (N=236)			
EGb group	-0.2 (-1.2 to 0.8) [104]	-0.09 (-0.16 to -0.02) [104]	4.2 (4.1 to 4.4) [120]
Placebo group	1.5 (0.3 to 2.6) [103]	0.09 (0.02 to 0.17) [101]	4.2 (4.1 to 4.4) [116]
Treatment difference	-1.7 (-3.2 to -0.2)	-0.19 (-0.28 to -0.08)	0.0 (-0.2 to 0.2)
P	.02	<.001	.21

* CI indicates confidence interval; ADAS-Cog. Alzheimer's Disease Assessment Scale–Cognitive subscale; GERRI. Geriatric Evaluation by Relative's Rating Instrument; and CGIC, Clinical Global Impression of Change. The ADAS-Cog is a 70-point scale; the GERRI is a 5-point scale; and the CGIC is a 7-point ordinal scale.

Prior to analysis, the distributions of the continuous variables, ie, the change scores from baseline for the ADAS-Cog and the GERRI, were tested and met the assumptions of normality. Nonparametric methods were applied for noninterval variables. The baseline Mini-Mental State Examination score was used to create a severity index for cognitive impairment.[6,24-26] Age was recoded to groups of younger than 65 years, 65 to 80 years, and older than 80 years. Paired *t* tests or median tests were performed within groups to determine if change from baseline was different from zero on the ADAS-Cog, GERRI, and CGIC.

The primary efficacy analysis used an analysis of variance model, with end point value as the dependent variable and treatment, age, and severity of cognitive impairment as factors; another model used as factors treatment, center and severity to test for center effect. In each model, a test for interaction between factors was included. Since subjects could be removed from the study if they had a 1-point increase in the CGIC, this variable was used for testing efficacy only in the ITT analysis.

To describe the response in a manner more applicable to clinical practice, categorical variables defining positive and negative change were developed for the ADAS-Cog and the GERRI and analyzed by applying the method of cumulative logits.[27] For the ADAS-Cog, a magnitude of ±2- and ±4-point cutoffs were adopted in accord with a previous standard from the literature.[19,28-31] Because there were no guidelines for cutoff points for the GERRI, the lower and upper quartiles that bound the middle 50% of the distribution of the scores in the total population were selected (±0.2 points).

In addition to the core study on the total population, a separate analysis was performed exclusively with the AD patients. This was done for 3 reasons; first, they are a large, clinically important, well-defined, and relatively homogeneous population; second, the criteria for AD, as summarized in the *DSM-III-R* and the *ICD-10* and applied in this study, led to a high reliability of the diagnosis[32-34]; and finally, the AD subgroup of this study formed a majority of the total sample.

RESULTS

Patient disposition during the study is summarized in Figure 1. From a total of 327 patients enrolled in the study (251 patients with AD), 309 patients were included in the ITT analysis.

Of the 18 patients not included, 15 had no data after baseline, 2 had insulin-dependent diabetes,

and 1 had an unstable affective mood disorder that required multiple psychotropic drugs. The group that received EGb included 155 patients; however, 17 of them were not compliant with the EGb regimen and an additional 15 patients did not achieve a minimum of 12 weeks of treatment. Of the 244 ITT patients reaching the 26-week visit, 202 (97 for EGb and 105 for placebo) provided evaluable data and could be included in the evaluable end point analysis.

There were 236 patients with AD in the ITT analysis, randomized to EGb (n = 120) or placebo (n = 116). The pattern of change in group sizes during the treatment period was similar to that in the total population.

Patient characteristics at baseline were similar between treatment groups and are summarized in Table 1. The patient characteristics for the evaluable data set were almost identical to those for the ITT group except for slightly lower values for the ADAS-Cog (17.2 and 19.9 for EGb and placebo groups, respectively).

Efficacy Analysis and ITT Analysis

Because the ITT analysis was based on last observations after baseline carried forward to end point, regardless of the actual treatment length, the average elapsed time within the study was computed for each treatment group. The EGb group had an average end point of 38.6 weeks (95% confidence interval, 35.7-41.5 weeks) compared with 34.6 weeks for the placebo group (95% confidence interval, 31.7-37.4 weeks). This difference was most likely related to the unequal distribution of the dropout rate after the 26-week visit. Although a similar ratio of subjects withdrew from each treatment group before 26 weeks (33/155 for the EGb group and 33/154 for the placebo group), 28% (44/155) of the EGb group vs 40% (62/154) of the placebo group dropped out between 26 and 52 weeks. Consequently, 50% (78/155) of the EGb group completed the entire study compared with only 38% (59/154) of the placebo group.

The results of the ITT analysis are provided in Table 2. In this table (as well as in Table 3, for the evaluable data set), the *P* values for treatment effects in change score are the results from the analysis of variance described in the "Methods" section. Although severity of cognitive impairment was a significant factor in overall change ($P<.01$) in all analyses, no significant interaction was found between severity and treatment. Furthermore, age was not a significant factor in any analysis and no interaction was found between treatment group and center.

Regarding the ADAS-Cog, there was no significant change observed at end point for the EGb group, whereas the placebo group showed a significant worsening of 1.5 points ($P = .006$). The mean treatment difference significantly favored EGb ($P = .04$). Considering the GERRI, mild improvement was observed for the EGb group, whereas the placebo group showed significant worsening (0.08 points; $P = .02$), resulting in a statistically significant difference in favor of EGb ($P = .004$). These results are depicted graphically in Figure 2. Regarding global psychopathology, a slight worsening was observed for both treatment groups on the CGIC (departure from a score of 4, "no change"; $P <.002$), as assessed by a deviation of 0.2 points of the rating mean (59% [183/309] of the total population were considered unchanged).

When the AD subgroup was examined separately, a similar pattern of results was demonstrated across the 2 treatments; differences were significant on both the ADAS-Cog ($P = .02$) and the GERRI ($P <.001$) (Table 2).

Evaluable Population

At the 26-week time point (Table 3), a slight improvement was observed in the EGb group on the ADAS-Cog while the placebo group showed a significant worsening of 1.4 points ($P =.002$). The mean treatment difference was in favor of EGb ($P =.04$). On the GERRI, the EGb group showed a mean improvement (0.07 points) and the placebo group worsened by the same amount, resulting in a statistically significant treatment difference ($P =.04$).

For the evaluable 52-week end point analysis, the average timing of the end point was 46.6 weeks (95% confidence interval, 44.1-49.0 weeks) for the EGb group and 42.3% weeks (95% confidence

Table 3. – Primary Outcome Measure Results: Evaluable 26-Week Time Point and 52-Week End Point Analyses *

	ADAS-Cog, Mean (95% CI) [n]		GERRI, Mean (95% CI) [n]	
	26 wk	52 wk	26 wk	52 wk
All diagnostic groups (N=202)				
EGb group	-0.5 (-1.6 to 0.6) [95]	-0.3 (-1.3 to 0.8) [96]	-0.07 (-0.13 to 0.00) [85]	-0.09 (-0.17 to 0.02) [89]
Placebo group	1.4 (0.3 to 2.5) [102]	2.1 (0.9 to 3.4) [104]	0.07 (-0.02 to 0.16) [85]	0.10 (-0.01 to 0.19) [88]
Treatment difference	-1.9 (-3.4 to -0.3)	-2.4 (-4.0 to -0.8)	-0.14 (-0.25 to -0.02)	-0.19 (-0.31 to -0.07)
P	.04	.005	.04	.002
Alzheimer disease (N=150)				
EGb group	-0.7 (-2.0 to 0.6) [74]	-0.5 (-1.7 to 0.8) [75]	-0.08 (-0.16 to 0.01) [64]	-0.08 (-0.17 to 0.01) [67]
Placebo group	1.4 (0.2 to 2.6) [73]	2.1 (0.7 to 3.5) [75]	0.07 (0.03 to 0.17) [63]	0.12 (0.01 to 0.22) [65]
Treatment difference	-2.1 (-3.8 to -0.3)	-2.6 (-4.4 to -0.7)	-0.15 (-0.28 to -0.02)	-0.20 (-0.33 to -0.06)
P	.02	.005	.05	.004

* Cl indicates confidence interval; ADAS-Cog. Alzheimer's Disease Assessment Scale–Cognitive subscale; GERRI. Geriatric Evaluation by Relative's Rating Instrument. The ADAS-Cog is a 70-point scale; the GERRI is a 5-point scale.

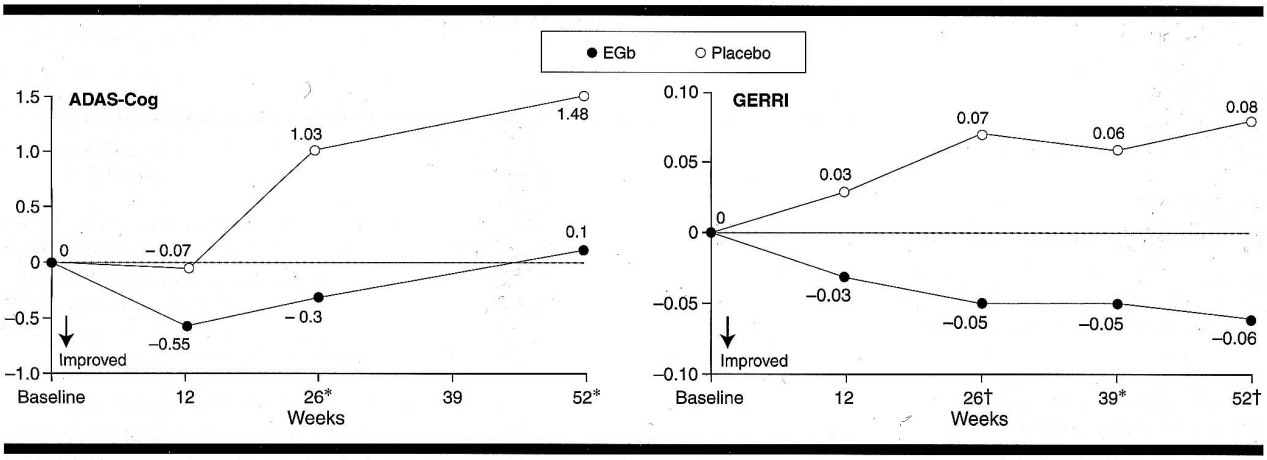

Figure 2. - Mean change in the primary outcome measures for the intent-to-treat analysis. Results of Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and Geriatric Evaluation by Relative's Rating Instrument (GERRI) at 12-, 26, 39-, and 52-week end points with last observation carried forward. Statistically significant differences between treatment groups are $P<.05$ (asterisk) and $P<.01$ (dagger).

interval, 39.8-44.8 weeks) for the placebo group. The difference of 4 weeks between these 2 end points followed the same pattern observed in the ITT analysis: in the EGb group, 71% (69/97) of the patients reaching 26 weeks completed the whole study compared with 51% (54/105) in the placebo group. The outcomes of the 52-week end point analysis are summarized in Table 3. There was a slight improvement for the EGb group on the ADAS-Cog, while the placebo group showed continued worsening, with an increased score from 1.4 at 26 weeks to 2.1 points at end point ($P<.001$). The mean treatment difference of -2.4 points further favored the EGb group ($P=.005$). The same course of changes were observed with the caregiver assessment. The EGb group showed significant improvement ($P=.02$) while the placebo counterpart deteriorated ($P=.04$), resulting in a statistically significant difference of -0.19 points for the GERRI change score ($P=.002$).

Categorical Analysis of Positive and Negative Outcomes

To compare the number of patients showing positive or negative clinical outcomes within each treatment arm of the evaluable data set, a cumulative logit analysis was conducted using the 52-week end point on the ADAS-Cog and the GERRI classification codes described in the "Methods" section. The results are summarized in Table 4. EGb shows a higher percentage of "improvers," while the placebo shows more "decliners," leading of highly significant differences on each assessment measure. On the ADAS-Cog, 50% of the EGb patients showed an improvement by at least 2 points compared with 29% of the placebo

Table 4. – Distribution of Improvers and Decliners in the Evaluable Population*

	ADAS-Cog						GERRI			
	n	-4 or Better	-2 or Better	+2 or Worse	+4 or Worse	*P*	n	Improved	Worse	*P*
All diagnostic groups (N=202)										
EGb group	96	26 (27)	48 (50)	30 (31)	21 (22)	.005	89	33 (37)	17 (19)	.003
Placebo group	104	15 (14)	30 (29)	48 (46)	33 (32)		88	20 (23)	35 (40)	
Alzheimer disease (N=150)										
EGb group	75	22 (29)	40 (53)	23 (31)	16 (21)	.006	67	26 (39)	15 (22)	.006
Placebo group	75	10 (13)	21 (28)	35 (47)	24 (32)		65	13 (20)	27 (42)	

* Data are given as number (percent) of patients. ADAS-Cog indicates Alzheimer's Disease Assessment Scale-Cognitive subscale; GERRI, Geriatric Evaluation by Relative's Rating Instrument.

group; this approximately 2-fold difference was still observed when the threshold to detect an improvement in cognition was set at 4 ADAS-Cog points. On the GERRI, 37% of the EGb group were considered improved and only 19% were considered worse; the placebo group demonstrated the opposite trend with 40% worsening and 23% improving.

Safety

Five serious adverse events were reported during the study: 3 deaths (1 in the placebo group and 2 in the EGb group) due to acute intercurrent conditions not related to the study medication, and 1 stroke and 1 subdural hematoma (both in the placebo group) related to worsening of preexisting condition. Thirty percent (49/166) of the patients in the EGb group reported at least 1 adverse event compared with 31% (50/161) in the placebo group. When only events related to study drug were considered, 16% (27/166) of the patients in the EGb group attributed at least 1 adverse event to the study drug compared with 12% (19/161) in the placebo group. Of 188 adverse events, 97 occurred with EGb and 91 with placebo. The majority of these adverse events (167/188) were considered of mild to moderate intensity. The adverse events of severe intensity (12 for EGb, 9 for placebo) were transient and resulted in withdrawal from the trial in only 2 patients receiving EGb and 1 receiving placebo. The adverse events, regrouped in their respective anatomicophysiologic systems, were equally distributed between the 2 treatment groups with the exception of the gastro-intestinal tract signs and symptoms being attributed slightly more often to EGb (18 of 29 events).

COMMENT

This study compared the effects of EGb with a placebo in a multicenter sample of demented patients with mild to moderately severe cognitive impairment. The results obtained from the ITT analysis and from the evaluable data demonstrated the efficacy of EGb on 2 of 3 primary outcome measures: cognitive impairment and daily living and social behavior. Although the treatment effect could not be detected by the clinician's global impression of change (CGIC), it was demonstrated through objective tests of cognitive performance (ADAS-Cog) and was of sufficient magnitude for the caregiver to recognize it in the patient's behavior (GERRI).

A concern in interpreting the study outcomes, however, relates to the substantial number of patients who withdrew after the 26-week visit. To reduce the potential bias due to the attrition of the randomization sample, the efficacy analysis was primarily based on ITT methodology. The ITT analysis, however, carries its own limitation. Dementia is inherently a deteriorating disease. By replacing missing data at end point with carried-forward values obtained early in the trial, the magnitude of the natural deterioration is underestimated; furthermore, different elapsed times in the study will tend to influence the effect size and possibly favor the group with the earliest end point. In the present sample, the EGb group included 50% of patients reaching the 52-week visit compared with only 38% of patients in the placebo group. Moreover, the average time of the end point occurred slightly earlier (4 weeks) for the placebo group. Despite these differences, apparently favorable to the placebo group, the ITT analysis showed that the EGb group maintained its baseline status (ADAS-Cog) or even improved slightly (GERRI), whereas both cognitive and social functioning worsened over time in the placebo group. These differences were observed even though 11% of the patients in the EGb group were not compliant with the drug regimen

and 10% were treated with EGb for less than 12 weeks. The ITT and evaluable analyses showed EGb to be more effective, but these analyses do not completely resolve the uncertainty of the effects that may arise from nonrandom dropouts.

Of the 3 outcome measures, the CGIC failed to demonstrate a significant difference in the efficacy of the 2 treatments. Several factors may have contributed to this. First, the treatment effects may not have been large enough to allow a discrimination from placebo. Second, the CGIC appears to have low sensitivity for measurement of change in dementia over the long term. It asks the clinician to quantify the amount of change in the patient's condition compared with baseline. However, it is not a structured instrument nor is it guided by anchored criteria. Thus, its reliability suffers as the interval between the follow-up visit and the baseline evaluation increases,[35] particularly if relevant information is not systematically elicited at each follow-up visit. The problem with its sensitivity as an outcome measure in AD surfaced in the earlier tacrine studies in which only the ADAS-Cog demonstrated an advantage for tacrine over the placebo.[31] The problem was partly remedied in more recent studies by replacing the CGIC with the Clinician Interview-Based Impression rating scale.[36] The latter apparently is a more reliable and sensitive guideline-based instrument, but one not yet available when the present study was initiated.

The failure to find differences using the CGIC, however, raised the question of whether the improvements in cognition and social behavior in the EGb group, although statistically significant, were sufficiently large to be "clinically meaningful." In this respect, the categorical analysis (Table 4) of the proportions of patients whose performance improved or worsened reflects more closely how the treatment effects are manifested clinically. In clinical terms, improvement on the ADAS-Cog of 4 points may be equivalent to a 6-month delay in the progression of the disease.[17,28,31] In this study, it is noteworthy that 29% of the patients with AD treated with EGb for at least 26 weeks improved by 4 or more points compared with 13% treated with the placebo (Table 4). These rations compare favorably with those obtained in a study of an evaluable group of patients with AD receiving a 30-week "high-dose" (160-mg) regimen of tacrine[31] (40% of the tacrine group improved by at least 4 points vs 25% of the placebo group).

The present trial, however, does not permit conclusions regarding sustained benefits, particularly if drug treatment is subsequently interrupted. In addition, this study tested a single EGb dose. It does not address whether the proportion of treatment responders will increase with higher dosages, as indicated by previous pilot studies,[37] or will remain the same but with an increase of the treatment effect. The latter finding would be more in accordance with the results obtained with 240 mg of EGb in a recent controlled trial in dementia.[13] Additional study testing multiple EGb dosages and applying a design that would distinguish a temporary stemming of the symptoms from a change in the course of the disease would be necessary to explore these important aspects.[38]

Owing to recent nosological developments[39,40] in the classification of vascular dementia (formerly MID), the frequent occurrence of mixed dementia (AD and vascular dementia), and the low clinicopathological correlation in postmortem analyses,[34] persons with MID as defined by DSM-III-R critera appear to be a heterogeneous group. Moreover, no specific neuropathological criteria for the neuroimaging findings were included in the present screening framework. Thus, in view of these limitations and of the relatively small number of patients with MID, the data of the vascular subgroup were not analyzed separately. Conversely, the results of the AD subgroup have been presented since its criteria have high reliability[32,33] and it represented the majority of the study sample. However, the present findings should be considered within the limits of our study population. The number of mildly impaired vs moderately and severly impaired patients may not be representative of the AD population at large. A sizable number of mild cases may have contributed to the fairly modest changes that were observed at end point. For example, the placebo group showed only a 1.5 point worsening on the ADAS-Cog score after an average elapsed time of 35 weeks, compared with 2.0- to 2.5 point changes observed with placebo groups of previous studies.[19,30,31] A pervasive learning effect also could be suspected in view of the relatively high percentage of improvers in the placebo group. Nevertheless, considering that the baseline characteristics of

the 2 treatment groups are similar and that there is no significant interaction between severity of impairment and treatment, EGb appears to stabilize and, in an additional 20% of cases (vs placebo), improve the patient's functioning for periods of 6 months to 1 year. Regarding its safety, adverse events associated with EGb were no different from those associated with placebo.

The EGb extract contains mulitple compounds that are thought to act synergistically on diverse processes involved in the homeostasis of inflammation and oxidative stress, providing membrane protection[3] and, neurotransmission modulation, which may be the basis for EGb effects at the central nervous system.[2,41,42] However, further research is needed to elucidate the precise mechanism of action of EGb, to fully explore the therapeutic potential of this plant extract, and to help better understand the pathogenesis of dementia.

The 6 US investigators who participated in the data collection of this project (The North American EGb Study Group) are Myron Brazin, MD, University of Medecine and Dentistry of New Jersey/New Jersey Medical School, Denville; James Ferguson, MD, Pharmacology Research Corporation, Salt Lake City, Utah; Alfred M. Freedman, MD, New York Medical College, Valhalla; Barry Jordan, MD, Cornell University Medical College, New York, NY; Joseph Mendels, MD, Philadelphia Medical Institute, Philadelphia, Pa (now with Therapeutics PC, Wynnewood, Pa); and Alan F. Schatzberg, MD, Harvard Medical Center, Boston, Mass (now with the School of Medicine, Stanford University, Stanford, Calif).

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