Original Article

Efficacy of rivastigmine in comparison to ginkgo for treating Alzheimer's dementia

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Abstract

Objectives: To assess the efficacy of the Ginkgo biloba in patients with dementia of the Alzheimer type in slowing down the disease's degenerative progression and the patients' cognitive impairment compared with rivastigmine.

Methods: Total 56 patients aged 50-75 years, suffering from dementia, were allocated into one of the two treatments: group 1) Ginkgo biloba (120 mg daily dose); group 2) rivastigmine (4.5 mg daily dose) in a 24-week randomized double blind study. The degree of severity of dementia was assessed by the Seven Minute test and the Mini-Mental State Examination.

Results: Our results confirm the clinical efficacy of rivastigmine in the dementia of the Alzheimer type, comparing to Ginkgo biloba. 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.

Conclusion: Our study suggests that there are differences in the efficacy of Ginkgo biloba and rivastigmine in the treatment of Alzheimer's dementia. In addition, this study suggested that cholinesterase inhibitors should be used in preference to Ginkgo biloba in patients with mild to moderate AD.

Keywords: Alzheimer, Dementia, Rivastigmine, Ginkgo biloba, Randomized trial. (JPMA 62: 677; 2012)

Introduction

Alzheimer disease (AD) is the most common form of dementia, accounting for more than one-half of new cases in Western countries.[1,2] Dementia is a generic term that describes the cognitive decline in brain function.[3] There are several causes of this condition, such as Alzheimer disease, head injury, Parkinson disease, Huntington disease, Creutzfeldt-Jakob disease Pick disease,. Some conditions that cause dementia are reversible, and others are not. The two most common forms of dementia in older people are AD that is irreversible.[4] The incidence of AD ranges from 1 to 4 percent of the population per year, rising from its lowest level at ages 65 to 70 years to rates that may approach 6 percent for those over the age of 85 years. The current estimates, all researchers agree that the number of AD cases will probably triple over the next 30 to 40 years.[5,6] AD is the most common form of dementia; it accounts for 64 % of all dementias.[7]

The clinical effects of a number of commonly used types of herbal medicines such as Ginkgo biloba for the treatment of AD have been discussed previously.[8] Ginkgo biloba extract has been used for thousands of years in traditional Chinese medicines for a variety of conditions. Recently, it has become more widely used in the United States to treat age-related physical and cognitive disorders.[9-11] Many studies in nursing home patients have also investigated the effects of rivastigmine on neuropsychiatric and behavioural symptoms associated with AD during different time courses.[12-15] The therapeutic efficacy of this extract is based on neuroprotective and metabolic effects. In addition to these mechanisms the hypothesis that dementia of Alzheimer's type is due to a cholinergic deficit at central synapses has led to the use of cholinesterase inhibitor. Thus nowadays, certain types of herbal medicines such as Ginkgo biloba extract are competing, on the synthetic side, with rivastigmine. The mechanism of action of Ginkgo is only partially understood, although the main effects seem to be related to its antioxidative properties, involving compound families in the herb, including flavonoids, terpenoids (ginkgolides, bilobalide), and organic acids.[12]

The aim of this study was to assess the effect of the Ginkgo biloba extract (EGb761) and rivastigmine in patients with dementia of the Alzheimer type in slowing down the disease's degenerative progress and the patient's cognitive impairment.

Patients and Methods

Following approval from the University Hospital

and Ahwaz Jundishapur University of Medical Sciences Ethics Committees and with written informed consent from the study participants, 56 patients aged 50-75 years, suffering from mild to moderate dementia, were allocated into one of the two treatment groups: Group 1) Ginkgo biloba (120 mg daily dose); Group 2) rivastigmine (4.5 mg daily). All participants were diagnosed as primary degenerative dementia of the Alzheimer type.

This was a double-blind, randomized, 24-week study with a withdrawal phase comparing Ginkgo biloba with rivastigmine in patients with mild to moderate AD. It was conducted from 2008-2009.

All subjects were randomized to ginkgo biloba extract (EGb761, Willmar Schwabe Pharmaceutical Co., Karlsruhe, Germany), 120 mg and matching rivastigmine tartrate (Exelon, Novartis Pharms co., Basel, Switzerland) 4.5 mg.

Inclusion criteria: Subjects were male or female, aged 50 to 75 years, with a diagnosis of probable AD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV),[16] and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[17] criteria and of mild to moderate severity, defined as a Mini-Mental State Examination (MMSE),[18] score of 10 to 24 at screening and Seven Minute Test (SMT).[18] The 7 Minute Screens consists of 4 tests representing 4 cognitive areas typically compromised in AD: (1) memory, (2) verbal fluency, (3) visuospatial and visuoconstruction, and (4) orientation for time. Each test (or modification of the test) was selected because previous research showed that it had a high degree of sensitivity to AD, could be rapidly administered by personnel with little training, and could be scored objectively.

Exclusion criteria were presence of any clinically significant or unstable medical condition or other mental problems as dermatologic, haematologic, pulmonary, cardiovascular, renal, hepatic, gastrointestinal, genitourinary, endocrine, or neurological disease (other than AD).

Discouraged from taking putative cognitive enhancers (such as ginkgo biloba, high-dose vitamin E, and non-steroidal anti-inflammatory drugs).

Medical conditions that could impact the bioavailability or metabolism of the study medications or affect the results of the study and patients with a current primary psychiatric diagnosis other than AD,

Patients who within the previous 5 years met DSM IV criteria for drug or alcohol abuse or dependence, or

With MMSE score of more than 24 at screening.

Also excluded were physically disabled patients, unable to hear/read instruction and motor deficits affecting writing and drawing

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 ± standard deviation (SD). A P value or less than 0.05 values was considered significant.

Results

At the end of the study, after 24 weeks of treatment period, 51 patients completed the trial. Of 56 subjects randomized for the study, 5 withdrew, three patients in the group 1 (20%) and two in group 2 (23%). In particular, in the group 1 the major cause of withdrawal was lost at follow-up and in group 2 in one case was the side effects and in the other case lost at follow-up was the cause for withdrawal. Demographic and baseline characteristics are shown in Table-1.

All values are expressed as mean change from baseline with standard deviation, considering the end of 24

Table-1: Demographic characteristics of patients included in the study.

Variables	All	Group1	Group 2
No. of Patients	51	25	26
Male	23 (45.1%)	12 (48%)	11 (42.3%)
Female	28 (54.9%)	13 (52%)	15 (57.7%)
Age (Years)	65.88 ± 4.63	65.72 ± 4.69	66.03 ± 4.64

Group 1) Ginkgo biloba-treated; group 2) rivastigmine - treated; Values represent mean ± standard deviation and number (%) of patients.

Table-2: baseline characteristics of patients included in the study.

Variables	Group1	Group 2	P-values (Between groups)
MMSE			
Base line	16.52 ± 4.12	16.58 ± 4.03	0.865
After 24 weeks	16.76 ± 4.34	17.53 ± 5.02	0.05*
P-values (Inside group)	>0.05	0.05*	
SMT			
Base line	213.76 ± 106.12	209.48 ± 107.48	0.601
After 24 weeks	212.96 ± 103.69	201.21 ± 102.71	0.05*
P-values (Inside group)	>0.05	0.05*	

Group 1) Ginkgo biloba-treated; group 2) rivastigmine - treated; Values represent mean ± standard deviation and number (%) of patients; MMSE, Mini-Mental State Examination; SMT, Seven Minute Test; * significant correlation.

weeks of treatment as the final time end-point. Regarding MMSE, we observed a statistically significant improvement of MMSE scores in the rivastigmine - treated ($P<0.001$), while in ginkgo biloba-treated groups the observation showed no significant difference ($P>0.05$): mean value was from 16.58 ± 4.032 at baseline to 17.54 ± 5.02 at 24 weeks period for rivastigmine - treated group and from 16.52 ± 4.124 to 16.76 ± 4.116 for Ginkgo biloba-treated group (Table-2). As regard SMT we observed a statistically significant improvement of SMT scores in the rivastigmine - treated ($P<0.001$), but in Ginkgo biloba-treated groups the observation showed no significant difference ($P>0.05$): mean value was from 209.48 ± 107.48 at baseline to 201.21 ± 102.71 at 24 weeks period for rivastigmine - treated group and from 213.77 ± 106.125 to 212.96 ± 103.69 for Ginkgo biloba-treated group.

Discussion

This study 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 evidence of relevant differences in the efficacy of Ginkgo biloba and rivastigmine in the treatment of mild to moderate Alzheimer's dementia. In addition, this study contributes to establish the efficacy and tolerability of the Ginkgo biloba in the dementia of the Alzheimer type with special respect to moderately severe stages. One of the most important parameters in demonstrating the clinical efficacy of an anti-dementia drug is the improvement in cognitive performance. MMSE and SMT are some of the most common instruments used in clinical evaluation of cognitive impairment. Our results confirm the clinical effect of Ginkgo biloba in the Alzheimer dementia that is comparable with rivastigmine clinical efficacy.

The MMSE has been largely used by other studies and has proved useful for this purpose.[20-22] The patient's attention, memory and cognitive performance after 24 weeks of treatment as measured by the MMSE test had shown a comparable important improvement compared with the rivastigmine-treated group. Therefore, the effectiveness of Ginkgo biloba can be confirmed by considering the significant group differences in MMSE score changes from the baseline to the final results. Solomon et al.,[23] 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.

There are few published trials that have directly compared a cholinesterase inhibitor with Ginkgo for dementia. As an example in agreement with the present study Kurz and Baelen,[30] have demonstrated that cholinesterase inhibitors such as rivastigmine are a better choice for improving AD tye of dementia during a 6 months. Besides, the study by Birks and Grimley Evans,[24] a Cochrane review of 35 clinical trials, suggested that Ginkgo biloba was ineffective for dementia, which addresses many weaknesses identified in previous studies by virtue of its large size and relatively lengthy duration (more than 6 years exposure to Ginkgo biloba). Parsons in a study showed that no evidence exists to support use of Ginkgo biloba to prevent dementia, which fits into the broader picture that Ginkgo biloba has no effect on slowing down progression of dementia in the early stages of disease.[25]

Recently Andrieu et al.,[26] in a study evaluated the efficacy of EGb761 (Ginkgo biloba) in the prevention of AD, and assessed the usefulness of various baseline characteristics as predictors of conversion to AD in this population. In another study Vellas et al.,[27] enrolled elderly 2851 subjects with spontaneous memory complaint and the primary outcome is the incidence of AD during a 5 years follow-up period, which showed the prevention of AD by EGb761. Lopez-Pousa and colleagues,[28] and Aguglia et al.,[29] conducted a study to determine the differential efficacy of the donepezil, rivastigmine, and galantamine with respect to a historical sample of AD patients that were not treated. After a study period of 6 months they found that all of the drugs significantly slowed the decline in cognitive function associated with AD.

Conclusion

This study contributes to establish the efficacy and tolerability of the Ginkgo biloba in dementia of the Alzheimer type not as good as rivastigmine. Considering the evidence, it is suggested that cholinesterase inhibitors should be used in preference to Ginkgo biloba in patients with mild to moderate AD.

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