

Combination Therapy of Donepezil and Vitamin E in Alzheimer Disease

*Emily T. Klatte, *Douglas W. Scharre, †Haikady N. Nagaraja, *Rebecca A. Davis,
and *David Q. Beversdorf

From the *Department of Neurology and †General Clinical Research Center, Ohio State University, Columbus, Ohio, U.S.A.

Summary: A retrospective chart review was performed on 130 patients from the Ohio State University Memory Disorders Clinic to examine the long-term effects of combination therapy with donepezil and vitamin E on patients with Alzheimer disease. Subjects were included if they met National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria for probable Alzheimer disease, had taken at least 5 mg donepezil and at least 1000 U vitamin E daily, had at least a 1-year follow-up while continuing these medications, and had a Mini-Mental State Examination score of 10–24. The Mini-Mental State Examination was then recorded annually thereafter. These data were compared with the Consortium to Establish a Registry for Alzheimer's Disease database for patients collected prior to the availability of these treatment options. Patients declined at a significantly lower rate as compared with the Consortium to Establish a Registry for Alzheimer's Disease data. The long-term combination therapy of donepezil and vitamin E appears beneficial for patients with Alzheimer disease. Future prospective studies would be needed to compare combination treatment to vitamin E and donepezil alone. **Key words:** Donepezil—Vitamin E—Mini-Mental State Examination.

Cholinesterase inhibitors augment cholinergic function by increasing synaptic acetylcholine concentration (Rogers et al., 1998). Patients with Alzheimer disease (AD) demonstrated cognitive benefits with several cho-

linesterase inhibitors, including donepezil, tacrine, rivastigmine, and galantamine (Doody et al., 2001a).

Donepezil improved Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) and Mini-Mental State Examination (MMSE) scores in patients with AD as compared with the placebo group in a 24-week study (Rogers et al., 1998). Cognitive improvements were maintained for 38 weeks over baseline with donepezil (Rogers and Friedhoff, 1998). Doody et al. (2001b) reported long-term benefits from donepezil in AD through an open-label, multicenter, phase III extension trial lasting up to 144 weeks. During this extension phase, however, inclusion of other agents such as vitamin E was allowed.

Vitamin E slows symptomatic progression in patients with AD, presumably because of interaction with free radicals and interruption of processes that result in cellular damage (Sano et al., 1997). In a 2-year, double-blind, placebo-controlled trial, vitamin E significantly

Received July 8, 2002. Accepted February 24, 2003.

This study was supported by an unrestricted educational grant from Pfizer/Eisai. The final pooled data from the Consortium to Establish a Registry for Alzheimer's Disease were used, obtained under NIA grant AG06790. Dr. Nagaraja is supported by a NIH grant (M01-RR-00034) awarded to Ohio State University.

Financial Disclosure: Dr. Scharre has grants from Janssen, Forest, and Pfizer; he is a consultant for Novartis, Janssen, and Pfizer; he is on the speaker's bureau for Janssen, Pfizer, Eisai, Abbott, and Astra-Zeneca. Dr. Beversdorf has grants from Pfizer and Eisai; he is a consultant for Janssen and Pfizer; he is on the speaker's bureau for Janssen, Pfizer, Eisai, and Novartis.

Address correspondence and reprint requests to David Q. Beversdorf, M.D., Means Hall 469, 1654 Upham Drive, Ohio State University Department of Neurology, Columbus, OH 43210, U.S.A. E-mail: beversdorf-1@medctr.osu.edu

delayed symptomatic progression including MMSE scores compared with placebo (Sano et al., 1997). Further evidence supports decreased risk of AD with dietary vitamin E intake (Morris et al., 2002).

A number of other agents have been explored for potential preventative or treatment roles in AD, but no systematic studies have examined combination therapy with these agents. According to the Quality Standards Subcommittee of the American Academy of Neurology, cholinesterase inhibitors are a standard in management of dementia and vitamin E is a guideline in the management of dementia (Doody et al., 2001a). Because cholinesterase inhibitors and vitamin E act through distinct mechanisms of action, benefits would be expected with combination therapy. However, cholinesterase inhibitors and vitamin E could interfere with each other and yield no benefit. No long-term study has examined this combination. The Ohio State University Cognitive Neurology Clinic has long-term experience with patients on this drug combination. Our purpose, therefore, is to determine whether donepezil and vitamin E combined slows the course of AD. Comparison with historical data with donepezil alone is not possible because the 3-year study of donepezil did not exclude patients taking vitamin E (Doody et al., 2001b). Rather, combination therapy with donepezil and vitamin E will be compared with historical data with no treatment.

METHODS

A retrospective chart review was performed on 130 patients from the Ohio State University Memory Disorders Clinic followed in the clinic between 1997 and 2001. Subjects were included if they met National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria for probable AD (McKhann et al., 1984), had taken donepezil at least 5 mg daily and vitamin E at least 1000 U daily, and had at least 1-year follow-up while using both of these medications. Fifty-six subjects met these criteria. Exclusion criteria included diagnosis with another form of dementia, failure to continue donepezil or vitamin E, or concurrent use of a third AD medication. None of the subjects with adequate follow-up was excluded for failure to continue treatment, but several were excluded due to use of a third AD medication.

Age, gender, education, medical history, and medications and their dosages were recorded. MMSE and Clinical Dementia Ratings were recorded at the initial visit, and MMSE was recorded at the beginning of therapy with donepezil and vitamin E, and annually for 3 years

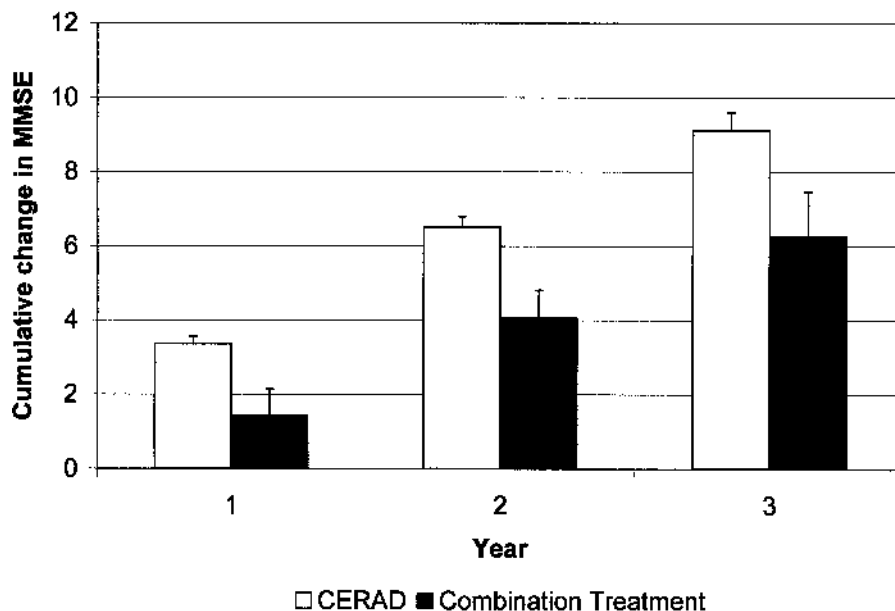
after initiation of therapy, administered in a uniform manner. Cumulative change in MMSE was calculated annually for 3 years after initiation of therapy for comparison with the 1986–1996 Consortium to Establish a Registry for Alzheimer's Disease (CERAD) database (Morris et al., 1989), collected prior to availability of these treatment options. Average age (\pm standard deviation) was slightly higher than for the CERAD group (73.6 ± 8.5 years vs. CERAD 70.9 ± 8.0 , $p = 0.02$). There was no significant difference in educational level (13.1 ± 3.8 years vs. CERAD 13.1 ± 3.2 , $p =$ not significant). Both groups demonstrated moderate female predominance (60.7% female vs. CERAD 54% female). Subjects from both groups with initial MMSE scores between 10 and 24 were compared using an independent samples t test. Forty from our clinic and 611 from the CERAD data qualified for the comparison study. At first presentation to the clinic, both the Clinical Dementia Rating and MMSE scores indicated milder impairment than the CERAD group (mean of Clinical Dementia Ratings 0.91 ± 0.36 vs. CERAD 1.41 ± 0.55 , $p < 0.0001$; MMSE 21.0 ± 4.7 vs. CERAD 18.7 ± 4.5 , $p = 0.00048$). However, the assessment at initiation of treatment was used in all subsequent analysis for our group.

RESULTS

Of the 40 subjects qualified, 40 had 1-year follow-up, 38 had 2-year follow-up, and 22 had 3-year follow-up.

At initiation of treatment, a trend remained for milder impairment in our group compared with the CERAD group (MMSE 19.5 ± 3.9 vs. CERAD 18.3 ± 3.9 , $F_{649} = 3.76$, $p = 0.053$). Average cumulative change in MMSE after 1, 2, and 3 years of therapy with donepezil and vitamin E was 1.43 ± 4.19 , 4.05 ± 4.75 , and 6.27 ± 5.68 , respectively (Fig. 1). Average cumulative change in MMSE for the CERAD group after 1, 2, and 3 years was 3.36 ± 4.57 , 6.51 ± 5.36 , and 9.12 ± 6.01 , respectively. The group receiving donepezil and vitamin E performed significantly better than the CERAD group on MMSE average cumulative change at the 1-year follow-up after initiation of combination therapy ($t_{585} = -2.595$, $p = 0.0097$, $n = 40$, and 547 CERAD), at the 2-year follow-up ($t_{347} = -2.696$, $p = 0.0074$, $n = 38$, and 310 CERAD), and at the 3-year follow-up ($t_{174} = -2.088$, $p = 0.0382$, $n = 22$, and 153 CERAD). These findings remained significant when groups were compared while adjusting for age and MMSE at the outset of treatment using analysis of covariance (1-year $F = 6.85$, $p = 0.0091$; 2-year $F = 7.13$, $p = 0.0080$; 3-year $F = 5.38$, $p = 0.0216$). Therefore, the average MMSE of patients on donepezil and vitamin E declined at a sig-

FIG. 1. Cumulative decline in Mini-Mental State Examination scores (\pm standard error) at years 1, 2, and 3 for the CERAD patients and patients treated with the combination of vitamin E and donepezil.



nificantly lower rate at the 1-, 2-, and 3-year follow-up as compared with the CERAD data (Fig. 1).

DISCUSSION

Rates of decline in this study are significantly better than in the CERAD data, suggesting in this retrospective study that combination therapy with donepezil and vitamin E is effective for slowing cognitive decline in patients with AD. Therefore, donepezil and vitamin E, which likely act through distinct mechanisms of action, probably do not interfere with each other in the treatment of AD. They may act synergistically, and when combined, offer benefit for patients with AD. However, comparison with data from long-term studies of patients on donepezil alone is not possible as is described above.

In our retrospective study, patients with poor outcomes in response to treatment might have been excluded secondary to the lack of follow-up. CERAD study dropouts could not have been due to poor treatment response. This could result in a selection bias. Other changes in care, such as availability of less sedating behavior management medications or any number of other differences in cohorts, may have influenced our results in comparison with the older CERAD data, generated when therapeutic nihilism was common for AD. Furthermore, a number of subjects in the CERAD database may have been taking vitamin E. Whereas this may also impact our results, it may be argued that it would narrow differences between groups. The greater age of our sample as compared with the CERAD group may have also contributed

to the slower rate of decline in our study sample (Mendiondo et al., 2000).

There are inherent limitations to a retrospective historical case-control study such as ours. Prospective trials comparing combination therapy of donepezil and vitamin E with the single drugs would be informative. However, such prospective studies might be difficult at this time because of the widespread accepted use of these two agents.

Several other agents have been postulated to benefit patients with AD. Because many of these medications may also act through distinct mechanisms, future prospective studies are needed to systematically examine further treatment combinations before they also become established treatment options. This will help with the understanding of the combinations of multiple agents that may be required to achieve optimal benefit in slowing the rate of cognitive decline associated with AD.

REFERENCES

- Doody RS, Geldmacher DS, Gordon B, et al. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. *Arch Neurol* 2001a;58:427-33.
- Doody RS, Stevens JC, Beck C, et al. Practice parameter: management of dementia (an evidence based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001b;56:1154-66.
- McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force of Alzheimer's Disease. *Neurology* 1984;34:939-44.
- Mendiondo MS, Ashford JW, Kryscio RJ, et al. Modelling Mini-Mental State Examination changes in Alzheimer's disease. *Statist Med* 2000;19:1607-16.

- Morris MC, Evans DA, Bienias JL, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA* 2002;287:3230–7.
- Morris JC, Heyman A, Mohs RC, et al. The consortium to establish a registry for Alzheimer's disease (CERAD): I. Clinical and neuropsychological assessment. *Neurology* 1989;39:1159–65.
- Rogers SL, Friedhoff LT. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: an interim analysis of the results of a US multicenter open label extension study. *Eur Neuro-psychopharmacol* 1998;8:67–75.
- Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998;50:136–44.
- Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997;336:1216–22.