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Alzheimer's & Dementia 10 (2014) 36–44

Alzheimer's & Dementia

Vitamin E and memantine in Alzheimer's disease: Clinical trial methods and baseline data

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Abstract

Background: Alzheimer's disease (AD) has been associated with both oxidative stress and excessive glutamate activity. A clinical trial was designed to compare the effectiveness of (*i*) alpha-tocopherol, a vitamin E antioxidant; (*ii*) memantine (Namenda), an N-methyl-D-aspartate antagonist; (*iii*) their combination; and (*iv*) placebo in delaying clinical progression in AD.

Methods: The Veterans Affairs Cooperative Studies Program initiated a multicenter, randomized, double-blind, placebo-controlled trial in August 2007, with enrollment through March 2012 and follow-up continuing through September 2012. Participants with mild-to-moderate AD who were taking an acetylcholinesterase inhibitor were assigned randomly to 2000 IU/day of alpha-tocopherol, 20 mg/day memantine, 2000 IU/day alpha-tocopherol plus 20 mg/day memantine, or placebo. The primary outcome for the study is the Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory. Secondary outcome measures include the Mini-Mental State Examination; the Alzheimer's Disease Assessment Scale, cognitive portion; the Dependence Scale; the

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http://dx.doi.org/10.1016/j.jalz.2013.01.014

Neuropsychiatric Inventory; and the Caregiver Activity Survey. Patient follow-up ranged from 6 months to 4 years.

Results: A total of 613 participants were randomized. The majority of the patients were male (97%) and white (86%), with a mean age of 79 years. The mean Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory score at entry was 57 and the mean Mini-Mental State Examination score at entry was 21.

Conclusion: This large multicenter trial will address the unanswered question of the long-term safety and effectiveness of alpha-tocopherol, memantine, and their combination in patients with mild-to-moderate AD taking an acetylcholinesterase inhibitor. The results are expected in early 2013.

Keywords: Alzheimer's disease; Alpha-tocopherol; Vitamin E; Memantine; Cholinesterase inhibitors; Randomized trials

1. Introduction

Cognitive impairment, functional decline, and behavioral symptoms that characterize Alzheimer's disease (AD) are associated with brain cholinergic loss [1], oxidative stress [2], and excessive glutamate activity [3,4]. Current therapeutic strategies include efforts to enhance cholinergic neuronal function with an acetylcholinesterase inhibitor(AChEI), promote neuroprotective effects with the administration of an antioxidant, and block pathological activity of excessive glutamate with a moderate-affinity N-methyl-D-aspartate (NMDA) antagonist. A combination of pharmacological therapies is potentially more effective than individual treatments alone. To test this hypothesis, this study examines the effectiveness of drug treatment in AD patients already taking an AChEI with (*i*) alpha-tocopherol (vitamin E), a fat-soluble vitamin and antioxidant that has been shown to slow the rate of progression of moderately severe AD [5]; and (*ii*) memantine (Namenda), a moderate-affinity NMDA antagonist that blocks excessive stimulation of NMDA receptors by glutamate [6] and is approved by the Food and Drug Administration for the treatment of moderately severe AD.

2. Methods

2.1. Overview of study design

The Department of Veterans Affairs (VA) Cooperative Study Program (CSP) Trial of Vitamin E and Memantine in Alzheimer's disease (TEAM-AD)(CSP #546) was designed as a double-blind, placebo-controlled, randomized clinical trial to assess the efficacy of 2000 IU/day of alpha-tocopherol, 20 mg/day memantine (Namenda), and a combination of both in delaying clinical progression in patients with AD currently taking an AChEI. The target population was veterans with a diagnosis of possible or probable AD [7] of mild-to-moderate severity defined as a Mini-Mental State Examination (MMSE) total score between 12 and 26 inclusive [8]. Fig. 1 displays an overall schematic of the study design.

A total of 14 VA medical centers participated in the trial (the organizational structure and study personnel for the trial are listed in Appendix 1). The study protocol was approved by the institutional review board at each participating site and the human rights committee at the West Haven CSP Coordinating Center. The trial was monitored for efficacy and safety by an independent Data Monitoring Committee (DMC) and is registered on www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT00235716). All participants or their surrogates gave written informed consent prior to study participation.

2.2. Study hypotheses and objectives

The primary study hypothesis is that, compared with placebo, alpha-tocopherol and/or memantine will significantly delay clinical progression in mild-to-moderately demented patients with AD who are currently taking an AChEI (donepezil [Aricept], rivastigmine [Exelon], or galantamine [Razadyne]) and that combination treatment with alpha-tocopherol and memantine will add further incremental benefit. Secondary study hypotheses are that alpha-tocopherol, memantine, and the combination will slow cognitive decline, slow functional decline, improve behavioral symptoms, and reduce caregiver burden, all relative to placebo.

2.3. Treatment regimens

Eligible patients who were currently taking an AChEI were assigned randomly to either 2000 IU/day alpha-tocopherol plus a matching placebo for memantine, 20 mg/day memantine (Namenda) plus a matching placebo for alpha-tocopherol, the combination of these two agents, or matching placebos for both memantine and alpha-tocopherol.

Alpha-tocopherol (or matching placebo) was given as an oral dose of 1000 IU twice a day. Dosage adjustments were allowed depending on participants' tolerability of the regimen. The form of vitamin E used in this study was dl-alpha-tocopheryl acetate (synthetic vitamin E) formulated as hard-gelatin, liquid-filled capsules. Matching placebos for vitamin E were hard-gelatin, liquid-filled capsules containing soybean oil. Encapsulation of the oils was completed by the VA CSP Clinical Research Pharmacy Coordinating Center.

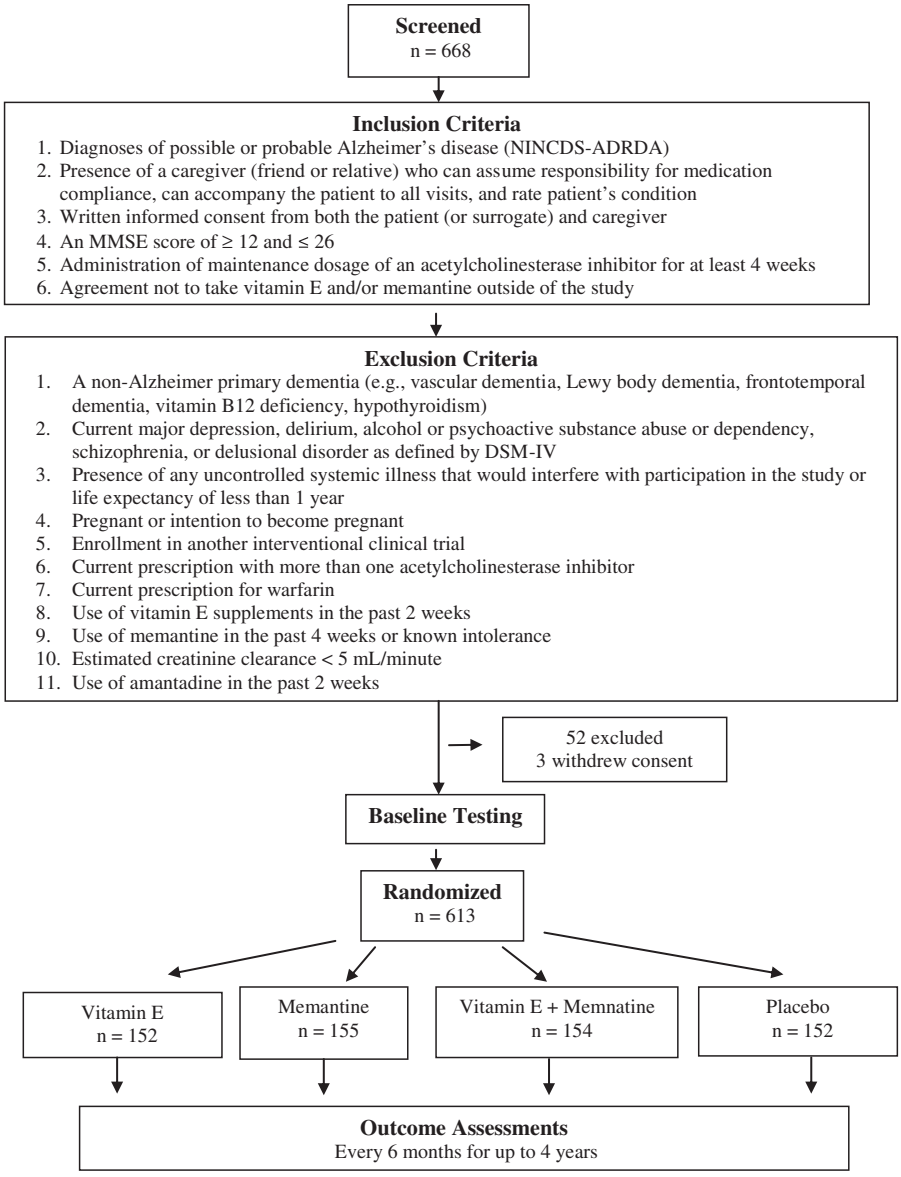

Fig. 1. Flow of participants in the study. NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; MMSE, Mini-Mental State Examination; DSM-IV, *Diagnostics and Statistical Manual of Mental Disorders*, 4th edition.

Memantine (or matching placebo) was titrated over 4 weeks to a maintenance dosage of 10 mg twice a day. At the end of the titration period, participants were taking four 5-mg tablets daily, two in the morning and two in the evening. For an individual whose estimated creatinine clearance at entry or during follow-up was less than 30 mL/minute, site investigators were directed to reduce the dosage of memantine (or matching placebo) to 5 mg twice daily. Other dosage adjustments by site investigators were discouraged but allowed based on participant tolerability.

2.4. Screening, baseline, and follow-up procedures

Screening data were collected on those patients who had signed consent or had begun formal screening. Many potential participants were excluded earlier, but these data were not collected because of patient privacy concerns and because doing so would increase the reporting burden on sites. Of the 55 patients who were excluded after signing the consent, the most frequent reasons were an MMSE score out of range (53%) and a life expectancy of less than 1 year (20%).

Potential subjects were identified at each site using institutional review board-approved procedures that included searching the VA electronic medical record, the VA pharmacy database, and the Decision Support System database. Site personnel also advertised the study with fliers, conducting in-service meetings, and contacting providers directly.

Baseline study assessments included a physical exam, a review of concomitant medication use, completion of the

primary and secondary outcome measures, and a blood draw for central laboratory storage and alpha-tocopherol and memantine serum concentration measures. All baseline assessments were performed prior to randomization.

Randomized participants were monitored every 6 months for a minimum of 6 months to a maximum of 4 years. Caregivers were contacted for a telephone interview for adverse events at 3 months after randomization. To encourage treatment adherence, participants and/or caregivers were also contacted by telephone at 1, 4, and 8 weeks to review the medication schedule and to discuss any concerns or questions that the participant and/or caregiver may have regarding the medications or the study.

2.5. Randomization and blinding

Eligible participants were randomized centrally by the coordinating center to one of the four treatment groups stratified by site using a random permuted block design of randomly varying sizes between 4 and 12. The treatment allocation ratio was 1:1:1:1. The patient, caregivers, and all site investigators were blinded to the treatment assignment.

2.6. Outcome measures

The primary end point of the study is the Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS/ADL) Inventory [9]. The ADCS/ADL Inventory is an informant-based measure of abilities to perform basic and instrumental ADLs in AD patients with a broad range of dementia severities. The ADCS/ADL Inventory was selected as the primary outcome measure because it is sensitive to multiple levels of functioning in AD, has substantial clinical relevance, and is more meaningful than cognition in measuring clinical progression [9–12]. Also, a patient's inability to perform ADLs may be more apparent to a caregiver than cognitive loss. Unlike global measures that rely on subjective judgment and have demonstrated inconsistent interrater reliability [13], the ADCS/ADL Inventory is based on scoring of specific questions posed to an informant; it has demonstrated excellent interrater reliability and it can be administered by a telephone interview with the caregiver.

The secondary outcome measures included the MMSE [8]; the Alzheimer's Disease Assessment Scale, cognitive subscale [14,15]; the Dependence Scale [16], a measure of the level of assistance needed by patients with AD; the 12-item Neuropsychiatric Inventory [17]; and the Caregiver Activity Survey [18].

All adverse events were recorded. Caregivers and patients were queried in general about adverse experiences at each contact, and were queried specifically about patient falls, syncope, and congestive heart failure diagnoses resulting from concerns from previous studies that these events could be related to high-dose alpha-tocopherol treatment [5,19].

2.7. Analytical plans

The original sample size for the study was 840 participants (210 per treatment group). This sample size was selected to provide 90% power to detect a 4-point mean treatment difference in the ADCS/ADL Inventory by the end of an average of 2.5 years of follow-up with a type I error of 0.0083 to control for six treatment comparisons and adjusted for 2.5% losses per 6-month follow-up. The original sample size was based on a repeated-measures analysis and used an estimated standard deviation (SD) of the ADCS/ADL Inventory of 12 units [12], and an estimated correlation of the repeated ADCS/ADL Inventory measurements within participants of 0.50. A re-estimation of sample size was conducted prior to the scheduled end of recruitment based on the observed variance and repeated-measures correlation of the ADCS/ADL Inventory as well as the observed loss rate. To preserve the type I error, the observed treatment effect was not used in the sample size re-estimation procedure.

Interim analyses for treatment efficacy of the primary end point were planned for at least two time points using the methods of Haybittle [20], but were designed to be flexible and allow the DMC to "look" on request. The final analysis of the primary end point will be by a longitudinal, repeated-measures mixed-effects model, adjusted for medical center as a random effect in the model and for the baseline ADCS/ADL Inventory score. The sequentially rejective procedure of Hochberg [21] will be used to control type I error for the six possible treatment comparisons using an overall type I error of 5% (two-sided).

3. Results

Between August 7, 2007, and March 31, 2012, a total of 668 veterans gave informed consent and were formally screened, and 613 were randomized: 152 to alpha-tocopherol alone, 155 to memantine alone, 154 to alpha-tocopherol plus memantine, and 152 to placebo (Fig. 1). The most common reason for exclusion was an MMSE score out of the acceptable range of 12 to 26 (53% of those excluded).

In January 2011, the DMC was presented with the final sample size re-estimation, which included an observed variance of 12.1 of the mean ADCS/ADL Inventory from the planned model, an observed correlation of 0.57 of the repeated ADCS/ADL Inventory measurements within participants, and an observed loss rate of 7.8% per 6 months of follow-up. Based on these observations and an extension of the enrollment period of 1.5 years and the follow-up period of 1 year, the sample size for the trial was re-estimated using the protocol hypothesized treatment effect of 0.8 units/6 months. The study extension increased the median follow-up from 2.5 years to approximately 3 years, and thereby increased the estimated overall treatment effect to 4.8 units over 3 years and the composite effect size (adjusted

for attrition) from 37% to 45%. The re-estimated total sample size to maintain approximately 90% power was 600.

As expected in a sample of VA patients with mild-to-moderate AD, most veterans were male (97%). The mean and median age at enrollment was 79 years (SD, 7.1 years) with a range of 53 to 96 years. Notable positive clinical histories included glaucoma or cataracts (36%), diabetes (27%), emotional problems (27%), musculoskeletal problems (27%), and heart disease (24%). The mean Charlson Risk Index score [22] at entry was 2.5 (SD, 1.7), and the majority of participants (54%) had ≥ two comorbidity domains on the Kansas City Stroke Study Comorbidity Disease Index [23,24] (Table 1).

A total of 612 patients (99.8%) were on an AChEI at baseline. Donepezil and galantamine were the most commonly prescribed AChEIs at 65% and 32%, respectively. The mean number of weeks from any AChEI initiation to randomization was 53 weeks (SD, 66 weeks; Table 2).

The overall mean score for the ADCS/ADL Inventory was 56.8 (SD, 14.2), ranging from 8 to 78. The overall mean score for the MMSE was 21.0 (SD, 3.6), ranging from 12 to 26 (the range of eligibility for the study; Table 3). The means for the Alzheimer's Disease Assessment Scale, cognitive subscale; Neuropsychiatric Inventory, and Caregiver Activity Survey were 18.8 (SD, 8.4), 12.5 (SD, 13.4), and 6.8 (SD, 10.9), respectively. The most frequent stages of dependence were levels 2 (55%) and 3 (22%).

Table 1
Demographic and clinical characteristics of randomized participants

Entry characteristic (n = 613)	Overall
Age, years; mean (SD), minimum–maximum	78.8 (7.1), 53–96
Male sex, n (%)	594 (97)
Race, n (%)*	
White	530 (86)
Black or African American	80 (13)
Other	4 (1)
Hispanic ethnicity, n (%)	66 (11)
Education, n (%)	
<High school graduate	137 (22)
High school graduate	207 (34)
Some college	135 (22)
College graduate or advanced degree	134 (22)
Body mass index, mean (SD)	26.7 (4.4)
Systolic blood pressure, mmHg; mean (SD)	134 (17)
Diastolic blood pressure, mmHg; mean (SD)	73 (11)
Laboratory values, n, mean (SD)	
International normalized ratio	590, 1.0 (0.3)
HDL cholesterol, mg/dL	608, 48 (15)
LDL cholesterol, mg/dL	605, 96 (32)
Total cholesterol, mg/dL	609, 169 (38)
Triglycerides, mg/dL	608, 131 (73)
Fasting glucose, mg/dL	610, 109 (36)
Homocysteine, μmol/dL	586, 13.6 (4.9)
Thyroid-stimulating hormone, μIU/mL	608, 2.1 (1.4)
Vitamin B12, pg/mL	607, 604 (322)
Creatinine clearance, mL/minute	612, 62.8 (22.7)
Creatinine clearance, <30 mL/minute; n (%)	23 (3.8)
Medical history, n (%)	
Glaucoma or cataract	222 (36)
Diabetes	167 (27)
Emotional problems	166 (27)
Musculoskeletal problems	166 (27)
Heart disease†	146 (24)
Sleep disorder	87 (14)
Cerebrovascular disease	61 (10)
Chronic pain syndrome	53 (9)
Peripheral vascular disease	50 (8)
Renal disease	28 (5)
Parkinson's disease	10 (2)
Smoker (current or past)	387 (63)
Charlson Risk Index score, mean (SD)	2.5 (1.7)
Comorbidity disease index, n (%)	
≤1 Domain	283 (46)
2 Domains	158 (26)
≥3 Domains	172 (28)

Abbreviations: SD, standard deviation; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Race and ethnicity were assessed in the study to demonstrate generalizability and to conduct possible subgroup analyses. Race and ethnicity were self-identified by study participants. More than one race was indicated by one participant.

†Heart disease includes a history of myocardial infarction, congestive heart failure, and/or angina.

4. Discussion

The Veterans Affairs TEAM AD was designed to assess the efficacy of 2000 IU/day alpha-tocopherol, 20 mg/day memantine, and their combination in delaying clinical progression in mild-to-moderately demented patients with AD. With the exception of a study sample composed predominantly of men, participants in CSP #546 are typical of patients enrolled in clinical trials of mild-to-moderate AD. The study will be one of the largest and longest treatment trials in patients with mild-to-moderate AD [25]. It will also be the first large-scale clinical trial to assess not only the effectiveness of alpha-tocopherol in patients with mild-to-moderate Alzheimer's dementia, but also the combination of alpha-tocopherol and memantine. In addition, the study will provide valuable information on reported safety issues of alpha-tocopherol [26] that have resulted in decreased prescribing of alpha-tocopherol for patients with AD [27].

The target population was veterans with a diagnosis of possible or probable AD whose level of dementia severity ranged from mild-to-moderate. This range of disease severity was selected because these are the patients who are most often diagnosed with AD and first started on medication by clinicians. The severity range was defined by an MMSE total score of 12 to 26. This range was selected because MMSE lower limit scores ranging from 10 to 14 have been used commonly in clinical trials to separate mild-to-moderate AD patients from those who are severely demented [28–30], and upper limit scores ranging from 24 to 26 have been used to separate mild-to-moderate AD patients from subjects with either mild

Table 2
Concomitant medications use at entry

Concomitant medications	n (%)
Acetylcholinesterase inhibitors	
Donepezil (Aricept)	400 (65)
Galantamine (Razadyne)	194 (32)
Rivastigmine (Excelon)	18 (3)
Weeks from AChEI initiation to randomization, n (%)	
≤12 weeks	170 (28)
>12 weeks	442 (72)
Statins	380 (62)
Aspirin	375 (61)
Antiplatelets, anticoagulants, or thrombolytics	43 (7)
Anticholinergics	26 (4)
Tertiary tricyclic antidepressants	18 (3)
Other antidepressants	213 (35)
Antipsychotics	37 (6)
Sedatives/hypnotics	37 (6)
Skeletal muscle relaxants	27 (4)
Vitamin C*	59 (10)
Other antioxidants†	122 (23)

Abbreviations: AChEI, acetylcholinesterase inhibitors.

*Fourteen participants were on vitamin C and at least one other antioxidant.

†Other possible antioxidants included vitamin A, vitamin B6, vitamin B12, folate, zinc, selenium, lycopene, and magnesium.

cognitive impairment or normal cognitive functioning [31–33].

The average length of follow-up for CSP #546 is considerably longer than most AD clinical trials [28–30,32,33]. In a Cochrane review of AChEI treatment in AD, most of the AD clinical trials (n = 12) averaged between 24 weeks and 26 weeks of follow-up, with only two trials that were a year (52 weeks) or longer (104 weeks) [34]. For the alpha-tocopherol/selegiline study in moderately severe AD patients [5], the trial duration was 2 years. In three recent memantine clinical trials in mild-to-moderate AD [35–37], the trial duration for each study was only 24 weeks. The knowledge gained from the relatively long-term follow-up in CSP #546 is an important component of the trial and will make the study results unique.

Table 3
Primary and secondary outcome assessments at entry

Assessments, range of scale	Mean (SD), Min–Max
Alzheimer's Disease Cooperative Study/activities of daily living, 0–78	56.8 (14.2), 8–78
Mini-Mental State Examination, 0–30	21.0 (3.6), 12–26
Alzheimer's Disease Assessment Scale, cognitive portion, 0–70	18.8 (8.4), 2.3–56
Neuropsychiatric Inventory, 0–144	12.5 (13.4), 0–95
Caregiver Activity Survey, 0–144 hours	6.8 (10.9), 0–144
Dependence Scale, n (%)	
Level 0	22 (4)
Level 1	27 (4)
Level 2	335 (55)
Level 3	134 (22)
Level 4	29 (5)
Level 5	66 (11)

Abbreviations: SD, standard deviation; Min, minimum; Max, maximum.

The long-term follow-up in an AD population has proved to be challenging. At the time of the last sample size re-estimation, the overall withdrawal rate was 31% and much greater than anticipated during study design. Nonetheless, the overall CSP #546 withdrawal rate at that time was comparable with withdrawal rates in 15 recently published clinical trials of shorter duration [25] in patients with similar AD severity. Among these 15 studies, the average withdrawal rate was 26%, with a range of 15% to 28%.

The trial was designed to provide 90% power to detect a 17.7% reduction in the annual rate of decline measured by the ADCS/ADL Inventory with each therapy given alone and, if the effects are additive, a 35% reduction for combined therapy by the end of the average follow-up period. The effect size chosen was relatively modest, yet was considered clinically important and would translate into slowing the rate of progression of the disease by nearly 6 months for monotherapy and 12 months for combined therapy [28–31]. The sample size re-estimation procedure used in the trial allowed for a slight reduction in the target sample size (820 to 800) based on a larger than expected correlation between repeated measures. This correlation helped overcome the need to increase the sample size based on the larger than expected loss rate. The observed SD was very similar to the original estimate and had almost no impact on the revised sample size. Although the sample size was reduced slightly, the primary reason for the reduction in the required sample size to 600 was as result of the increase in overall effect size with the increase in average follow-up time.

Re-estimating sample size during a trial can be very important, particularly in a study in which information about the nuisance parameters (e.g., variance and correlation) is not reliable. An observed parameter that is significantly different from the estimate can result in a substantially under- or overpowered study. For CSP #546, the differences in the observed vs the protocol estimates of the nuisance parameters led to a re-estimated sample size that was fairly similar to the original. In the end, the extension of participant follow-up was needed to reduce the sample size to a feasible target.

The original target sample size could not be achieved because of a lower than expected number of eligible patients, greater than anticipated staff workload to enroll and monitor patients, and higher than predicted patient and caregiver refusal rates. The primary reason for excluding potential participants who signed the informed consent was an MMSE score out of the acceptable range of 12 to 26 (53%); other prominent reasons for exclusions prior to data collection were warfarin use, current memantine use, overall caregiver burden, study pill burden, and concern

about the safety of high-dose alpha-tocopherol resulting from a published meta-analysis of the possible risk of alpha-tocopherol [26] and popular media coverage of the article.

During the enrollment period, the study's executive committee monitored recruitment closely and attempted to address issues when possible. For example, to encourage compliance with VA guidelines that memantine should only be prescribed for patients with moderate or severe disease (MMSE score <15), discussions were held with pharmacy managers within the participating VA medical centers. To reduce caregiver burden and stress, the committee encouraged site staff to connect caregivers to AD support groups and to help them navigate the VA system for other needed medical care. Research coordinators were encouraged to travel to patients' homes for follow-up visits whenever possible and to conduct follow-up assessments over the telephone if needed. Caregivers were provided published materials on AD and caregiving to help with patient management and reduction in caregiver stress.

The CSP #546 executive committee also monitored the study's withdrawal rate closely and attempted to address site-specific issues when possible. Some of the successful techniques used by participating sites to improve retention were assisting patients and caregivers in navigating the VA system, connecting patients and caregivers with VA social work services, scheduling study appointments in conjunction with other appointments at the medical center, and conducting study visits over the telephone or in a patient's home when possible.

On two occasions the executive committee discussed the results of the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which was designed to determine whether selenium (200 μg/day), vitamin E (400 IU/day), or the combination when compared with placebo prevented incident prostate cancer in older men. The study was discontinued in 2008 after a median follow-up of 5.5 years as a result of a recommendation by the Data and Safety Monitoring Board (DSMB) based on futility. At the time, 35,533 men had been enrolled and a nonsignificant increase in vitamin E-associated prostate cancer was found [38]. On the basis of the nonsignificant finding, it was decided that no action was necessary in either modifying the CSP #546 consent forms or informing patients and caregivers of the SELECT results.

After SELECT was discontinued, unblinded follow-up was continued from October 2008 until July 2011 [39]. The primary end point was prostate cancer incidence detected as the result of routine community care. With 54,464 additional person-years of follow-up, Klein and colleagues [39] reported a statistically significant increase in prostate cancer incidence in the vitamin E group (hazard ratio = 1.17). The CSP #546 executive committee compared the SELECT study with two other large, randomized prevention trials that examined the effects of vitamin E supplementation on prostate cancer risk. The Alpha-Tocopherol, Beta Carotene trial (ATBC) [40] reported a 35% risk reduction for prostate cancer in men taking 50 mg/day vitamin E for a median of 6.1 years. In the Physicians Health Study II (PHS II) [41], 400 IU vitamin E every other day for a median of 8 years had no effect on the incidence of prostate cancer. Based on a review of SELECT, ATBC, and PHS II, the committee concluded that the current overall evidence did not support a conclusion that there is a clinically significant increased risk of developing prostate cancer in CSP #546 participants taking vitamin E. With concurrence from the DMC and CSP Central Office, the committee recommended, however, that site investigators discuss with patients and caregivers the SELECT results in the context of the findings from PHS II and ATBC, and to do so at the next scheduled visit.

Although representative of the gender ratio for the veteran population, one limitation of the study is the small percentage of women. However, there is no reason to believe that alpha-tocopherol or memantine would have a different effect in males compared with females, and there is no evidence of this based on previous studies [5,10,11]. Another limitation is the higher than anticipated loss rate if that loss rate turns out to be related to the primary outcome, which is not implausible because losses resulting from caregivers' inability to manage patients, nursing home placement, and death could all be related to the functional and cognitive decline of the disease study itself over time.

The VA TEAM-AD study is a large multicenter trial that will address the unanswered question of the long-term safety and effectiveness of alpha-tocopherol, memantine, and their combination in patients with mild-to-moderate AD who are taking an AChEI. Publication of the results is expected in 2013.

Acknowledgments

The VA Trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM-AD)(CSP #546) was funded by the Department of Veterans Affairs Cooperative Studies Program. Forest Research Institute, a Division of Forest Laboratories, Inc., donated the memantine and matching placebo tablets. DSM Nutritional Products, Inc., donated the dl-alpha-tocopheryl acetate oil and funding for the purchase of the soybean oil from Arista Industries, Inc. The Department of Veterans Affairs Cooperative Studies Program, as sponsor of the trial, participated in the design and oversaw the conduct of the study but had no input into data collection, management, analysis, and interpretation of the data or preparation, review, or approval of the manuscript.

RESEARCH IN CONTEXT

1. Systematic review: We searched PubMed using the keywords vitamin E, alpha-tocopherol, memantine, Alzheimer's disease (AD), and clinical trial. Although vitamin E and memantine have been studied in AD patients, vitamin E has not been studied in mild-to-moderate AD, memantine trials in this group have been limited by short duration, and the combination has not been studied.
2. Interpretation: Cooperative Study Program (CSP) #546 represents one of the largest (n = 613) and longest (average follow-up, 3 years) randomized trials in AD. Challenges included the selection of outcome measures, minimizing the withdrawal rate, sample size re-estimation, and external information about treatment efficacy and safety.
3. Future directions: Because the study has excellent statistical power, the results will enable policymakers to decide whether vitamin E, memantine, or their combination should be prescribed in this group. The description and discussion of methods will be informative for the design of future AD studies longer than 1 year.

References

[1] Davies P. Studies on the neurochemistry of central cholinergic systems in Alzheimer's disease. In: Katzman R, Terry RD, Bick KL, eds. Alzheimer's disease: senile dementia and related disorders. New York: Raven Press; 1978. p. 453–9.

[2] Markesbery WR. The roles of oxidative stress in Alzheimer disease. Arch Neurol 1999;56:1449–52.

[3] Cacabelos R, Takeda M, Winblad B. The glutamatergic system and neurodegeneration in dementia: preventive strategies in Alzheimer's disease. Int J Geriatr Psychiatry 1999;14:3–47.

[4] Lipton SA, Rosenberg PA. Excitatory amino acids as a final common pathway for neurologic disorders. N Engl J Med 1994;330:613–22.

[5] Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, 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.

[6] Danysz W, Parsons C. The NMDA receptor antagonist memantine as a symptomatological and neuroprotective treatment for Alzheimer's disease: preclinical evidence. Int J Geriatr Psychiatry 2003; 18:S23–32.

[7] McKhann G, Drachman DD, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force in Alzheimer's disease. Neurology 1984;34:939–44.

[8] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res 1975;12:189–98.

[9] Galasko D, Bennet D, Sano M, Ernesto C, Thomas R, Gundman M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. Alzheimer Dis Assoc Disord 1997;11:S33–9.

[10] Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333–41.

[11] Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate-to-severe Alzheimer disease already receiving donepezil. JAMA 2004; 291:317–24.

[12] Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, et al., Alzheimer's Disease Cooperative Study. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 2003;289:2819–26.

[13] Oremus M, Perrault A, Demers L, Wolfson C. Review of outcome measurement instruments in Alzheimer's disease drug trials: psychometric properties of global scales. J Geriatr Psychiatry Neurol 2000; 13:197–205.

[14] Mohs RC, Rosen WG, Davis KL. The Alzheimer's Disease Assessment Scale: an instrument for assessing treatment efficacy. Psychopharmacol Bull 1983;19:448–50.

[15] Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–64.

[16] Stern Y, Albert SM, Sano M, Richards M, Miller L, Folstein M, et al. Assessing patient dependence in Alzheimer's disease. J Gerontol 1994;49:M216–22.

[17] Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi D, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–14.

[18] Davis K, Marin D, Kane R, Patrick D, Peskind E, Raskind M, et al. The Caregiver Activity Survey (CAS): development and validation of a new measure for caregivers of persons with Alzheimer's disease. Int J Geriatr Psychiatry 1997;11:978–88.

[19] Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue T, Arnold JM. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA 2005;293:1338–47.

[20] Haybittle JL. Significance testing in the comparison of survival curves from clinical trials of cancer treatment. Eur J Cancer Clin Oncol 1986; 22:1279–83.

[21] Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800–2.

[22] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

[23] Rigler SK, Studenski S, Wallace D, Reker DM, Duncan PW. Co-morbidity adjustment for functional outcomes in community-dwelling older adults. Clin Rehabil 2002;16:420–8.

[24] Studenski S, Lai SM, Duncan PW, Rigler SK. The impact of self-reported cumulative comorbidity on stroke recovery. Ageing 2004; 33:195–8.

[25] Grill JD, Karlawish J. Addressing the challenges to successful recruitment and retention in Alzheimer's disease clinical trials. Alzheimers Res Ther 2010;2:34.

[26] Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Int Med 2005;142:37–46.

[27] Dysken MW, Kirk LN, Kuskowski M. Changes in vitamin E prescribing for Alzheimer patients. Am J Geriatr Psychiatry 2009;17:621–4.

[28] Aisen PS, Schneider LS, Sano M, Diaz-Arrastia R, van Dyck CH, Weiner MF. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease. JAMA 2008;300:1774–83.

[29] Doody RS, Gavrilova SI, Sano M, Thomas RG, Aisen PS, Bachurin SO, et al. Effect of dimebon on cognition, activities of daily living, behavior, and global function in patients with mild-to-moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled study. Lancet 2008;372:207–15.

[30] Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer's disease: a randomized trial. JAMA 2011; 304:1903–11.

[31] Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, et al. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized trial. JAMA 2009;302:2557–64.
[32] Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, et al. Clinical effects of Aβ immunization (AN1792) in patients with AD in an interrupted trial. Neurology 2005;64:1553–62.
[33] Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, et al. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology 2009;73:2061–70.
[34] Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006;1:CD005593.
[35] Peskind ER, Potkin SG, Pomara N, Ott BR, Graham SM, Olin JT, et al. Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial. Am J Geriatr Psychiatry 2006;14:704–15.
[36] Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT, Memantine MEMMD-12 Study Group. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res 2008;5:83–9.
[37] Bakchine S, Loft H. Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. J Alzheimers Dis 2008; 13:97–107.
[38] Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009;301:39–51.
[39] Klein EA, Thompson IM Jr., Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2011;306:1549–56.
[40] The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029–35.
[41] Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA 2009;301:52–62.

Appendix 1

The following persons participated in the Veterans Affairs (VA) Trial of Vitamin E and Memantine in Alzheimer's Disease Planning Committee: S. Asthana, M. Dysken, P. Guarino, J. Hanlon, M. Kunik, P. Lavori, P. Peduzzi, E. Perry, M. Sano, G. Schellenberg, T. Sunderland, G. Vatassery†, J. Vertrees, and L. Volicer. The Executive Committee was comprised of M. Dysken (Chair), S. Asthana, P. Guarino, M. Llorente, S. Love, M. Pallaki, M. Sano, G. Schellenberg, G. Vatassery†, and J. Vertrees. The Data Monitoring Committee was comprised of K. Kieburtz (Chair), C. Kawas, E. Lonn (resigned), P. Rabins, J. Rochon, D. Sultzer, and R. Thomas. The VA Cooperative Studies Program Human Rights Committee, West Haven, CT, was comprised of R. Marottoli (Chair), H. Allore, D. Beckwith, W. Farrell, R. Feldman, R. Mehta, J. Neiderman, E. Perry, S. Kasl, and M. Zeman. The VA site investigators and coordinators included, in Ann Arbor, MI, R. S. Turner, J. Heidebrink, C. Bloehm, J. Lord, K. Belanger, N. Ricci, C. Nwankwo, C. Fletcher, and N. Barbas; in Baltimore, MD, D. Loreck, L. Katzel, K. Anderson, G. Kavanagh, S. Carney, and A. Loreck; in Bay Pines, FL, S. Reddy, N. Purohit, R. Tamayo, K. Monnell, A. Cruz, S. Huda, S. Zachariah, and W.C. McCarthy; in Boston, MA, N. Kowall, B. Seltzer, M. Chopra, and K. Kolbe; in Charleston, SC, J. Mintzer, O. Brawman-Mintzer, A. Senseney, D. Courtney, M. Stuckey, S. Russell, and J. A. Sweeney; in Cleveland, OH, M. Pallaki, P. Chen, T. Hornick, T. Dolinar, L. Abood, A. Coulter, S. Truax, and D. Davis; in Dallas, TX, R. Bakshi, G. Trapp, L. Moody, N. Flye, and D. Turner-Knight; in Iowa City, IA, C. Turvey, C. Woodman, A. Ray, K. Ekstam Smith, and N. Suiter; in Madison, WI, S. Asthana, C. Gleason, S. Barczi, C. Carlsson, N. Lane, M. Wroblewski, Z. Zugin, and J. J. Fruehling; in Miami, FL, M. Llorente, F. Adan, J. Malphurs, S. Prieto, M. Horvath, D. Santiago, G. Athappilly, A. Cortes, A. Vazquez, R. Dreize, F. Ostovary, E. Palaois, M. Oliveira, J. Pino, and L. Claude; in Minneapolis, MN, J. McCarten, H. Fink, C. Erickson, and L. Becker-Grandle; in Salisbury, NC, K. Monnell, K. Phillips, D. Eknoyan, and K. Gordon; in San Juan, PR, A. Vidal-Cardona, L. Arroyo, A. Melendez, L. Santiago, and B. Padilla; and in Seattle, WA, S. Craft, J. Breitner, S. Thielke, K. Enstrom, J. Tidwell, R. Bridgan, K. Bowton, and D. Dahl. The Study Chair's Office, VA Health Care System, Minneapolis, MN, included M. Dysken (Study Chair), S. Love, and J. Tomaska; the Central Laboratory, VA Health Care System, Minneapolis, MN, included G. Vatassery†, Y. Segal, and H. Quach; the VA Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven, CT, included P. Guarino (Director, Study Biostatistician), M. Antonelli, E. Jobes, C. Joncas, S. Joyner, K. Kirkwood, P. Peduzzi, M. Perry, E. Petrokaitis, J. Scholl, S. Yang, and S. Zellner; the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, NM, included M. Sather (Director), J. Vertrees, D. Conner, S. Campbell, S. Jenkins, and A. Davis; the VA Cooperative Studies Program Site Monitoring, Auditing and Review Team, Albuquerque, NM, included C. Haakenson and D. Krueger; the VA Cooperative Studies Program Laboratory MAVERIC , VA Healthcare System, Boston, MA, included M. Brophy (Director), D. Humphries, and D. Govan; VA Cooperative Studies Program DNA Bank Coordinating Center, VAMC Palo Alto, CA, included J. Cockroft, S. Bobra, A. Baylosis, and R. Dodson; the VA Office of Research and Development, Clinical Science R&D, Washington, DC, included T. O'Leary (Director, Deputy CRADO) and G. Huang (Deputy Director, Cooperative Studies Program).

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