A RANDOMIZED CONTROLLED ALZHEIMER’S DISEASE PREVENTION TRIAL’S EVOLUTION INTO AN EXPOSURE TRIAL: THE PREADVISE TRIAL

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FOR THE SELECT INVESTIGATORS


Abstract: Objectives: To summarize the ongoing Prevention of Alzheimer’s Disease (AD) by Vitamin E and Selenium (PREADViSE) trial as an ancillary study to SELECT (a large prostate cancer prevention trial) and to present the blinded results of the first year as an exposure study. Design: PREADViSE was designed as a double blind randomized controlled trial (RCT). Setting: SELECT terminated after median of 5.5 years of exposure to supplements due to a futility analysis. Both trials then converted into an exposure study. Participants: In the randomized component PREADViSE enrolled 7,547 men age 62 or older (60 if African American). Once the trial terminated 4,246 of these men volunteered for the exposure study. Demographics were similar for both groups with exposure volunteers having baseline mean age 67.3 ± 5.2 years, 15.3 ± 2.4 years of education, 9.8% African Americans, and 22.0% reporting a family history of dementia. Intervention: In the RCT men were randomly assigned to either daily doses of 400 IU of vitamin E or placebo and 200 µg of selenium or placebo using a 2x2 factorial structure. Measurements: In the RCT, participants completed the Memory Impairment Screen (MIS), and if they failed, underwent a longer screening (based on an expanded Consortium to Establish a Registry in AD [CERAD] battery). CERAD failure resulted in visits to their clinician for medical examination with records of these examinations forwarded to the PREADViSE center for further review. In the exposure study, men are contacted by telephone and complete the telephone version of the memory impairment screen (MIS-T) screen. If they fail the MIS-T, a Modified Telephone Interview of Cognitive Status (TICS-M) exam is given. A failed TICS-M exam also leads to a visit to their clinician for an in-depth examination and forwarding of records for a centralized consensus diagnosis by expert clinicians. A subgroup of the men who pass the MIS-T also take the TICS-M exam for validation purposes. Results: While this ancillary trial was open to all 427 SELECT clinical sites, only 130 (30.0%) of the sites chose to participate in PREADViSE. Staff turnover at the sites presented challenges when training persons unfamiliar with cognitive testing procedures to conduct the memory screens. In the RCT few participants (1.6%) failed the MIS screen and among those who passed this screen a significant practice effect was encountered. In the exposure study 3,581 men were reached by phone in year 1, 15.7% could not be reached after 5 calls, and of those contacted 6.0% refused the screen even after consenting to the procedures at their clinical site. Most notable is that the failure rate for the MIS-T increased fourfold to 7.2%. Of the 257 men who took the TICS-M, 84.0% failed and were asked to contact their physicians for a more detailed memory assessment, and approximately half of these had some form of dementia or cognitive impairment. Several of these dementia cases are not AD. Conclusion: Partnering with SELECT led to an AD prevention trial conducted at a very reasonable cost by taking advantage of the experience and efficient clinical trial management found in a cancer cooperative group (Southwest Oncology Group or SWOG). Once unblinded, the RCT and exposure study data have the potential to yield new information on long term exposure to antioxidant supplements under controlled conditions.

Key words: Alzheimer’s disease, prevention, telephone screening, cognitive assessments, case ascertainment.

Introduction

There is a need to develop prevention strategies for Alzheimer’s disease (AD) and other forms of dementia because treatment trials for these diseases have only provided modest symptomatic success and because there is an anticipated rise in the incidence of these diseases over the next few decades primarily due to the aging populations worldwide (1). Several prevention trials have been recently completed, all with null/inconclusive results (2-6). The purpose of this manuscript is to describe how a trial investigating supplements to prevent dementia had to be prematurely terminated for futility unrelated to cognition and converted into an exposure study. The term “exposure” refers to a follow-up on the cognitive status of individuals who have been exposed in blinded fashion to nutritional supplements or placebo for an average of 5 years.

The rationale for the Prevention of Alzheimer’s Disease (AD) by Vitamin E and Selenium (PREADViSE) trial is based on numerous animal models, human autopsy studies, several large observational studies, and at least one human AD clinical trial of vitamin E investigating the role of antioxidants in the disease process (7-9). Oxidative stress has been shown to be important in the pathophysiology of neuron degeneration and death in AD (10, 11).
The PREADViSE trial was leveraged as a cooperative study of a large multi-center prostate cancer prevention trial for healthy older men (SELECT) directed by SWOG, a federally funded cancer research cooperative group. This 2x2 factorial randomized clinical trial (RCT) was terminated after a median of 5.5 years of exposure due to a futility analysis (prostate cancer outcome) (12). It is now an exposure study of approximately half of its men who volunteered for centralized follow-up. Recent data based on 7-10 years of follow-up showed that men randomized in the vitamin E only arm had a significant 17% increase in the incidence of prostate cancer compared to the placebo arm. However, men randomized in the selenium only or selenium plus vitamin E arms did not incur significant increases in prostate cancer (13).

The specific aims of PREADViSE were to determine the effect of selenium and vitamin E used in combination or alone on the incidence of Alzheimer’s disease (AD) primarily and on the incidence of other neurodegenerative diseases secondarily. A third aim was to investigate the features of normal cognitive aging in a validation subsample. This manuscript describes PREADViSE in the context of an AD prevention trial as an ancillary study to a cancer prevention trial and presents the blinded results of the first year of its exposure study.

Materials and Methods

SELECT randomized 35,533 men in 34 months who were aged 55 or older (50 if African American) at 427 sites throughout the United States, Canada, and Puerto Rico. Men were randomly assigned to receive identical capsules: one containing 400 IU of vitamin E or placebo and the other containing 200 µg of selenium or placebo per day utilizing a 2x2 factorial double blind RCT design (14).

PREADViSE enrolled 7,547 of SELECT’s oldest men (age 62 or older; over age 60 if African American) at 128 of these sites. To be eligible for this study these men had to enroll at a SELECT site willing to participate in PREADViSE, sign a consent form specific to this ancillary study, and be free from dementia at baseline as evidenced by a passing score on the Memory Impairment Screen (MIS). Men with active neurologic conditions affecting cognition or with a history of major psychiatric disorder or substance abuse, and men on memory enhancement drugs were ineligible for this substudy (15).

PREADViSE used the following two-tiered screening system administered annually by trained clinical research assistants at SELECT study sites for identifying incident cases of dementia:

Tier 1: Memory Impairment Screen (16): a two-minute, four-item delayed free and cued recall memory test with controlled learning. A cut-score of four was suggested by the creators of the measure because it provided a high level of sensitivity (0.80), specificity (0.96), and positive predictive value (0.69) for most base rates of dementia. It was administered to all PREADViSE participants at baseline, then annually during follow-up using alternating versions of the test. Participants falling below the cut score also completed the second-tier evaluation.

Tier 2: An expanded Consortium to Establish a Registry for Alzheimer’s Disease (CERAD (17, 18)): a protocol comprising the CERAD battery of verbal fluency (Animal Naming), Boston Naming Test, Constructional Praxis, Mini-Mental State Exam, 10-item word list with immediate and delayed recall and recognition trials and supplemented by the NYU paragraph recall test, clock drawing, Geriatric Depression Scale, and the Short Blessed Test. This is the expanded CERAD battery (CERADe).

CERADe failures, defined as a CERAD T-score below 35, were advised to visit their physician for medical examination with records of these examinations forwarded to the PREADViSE coordinating center for further review. All participants were asked to donate a blood sample at baseline and 5 years post baseline; these samples were processed and stored at the SWOG biospecimen bank at the National Cancer Institute in Frederick, Maryland. In addition, a subset of the participants (n = 563) who passed the MIS also underwent the CERADe test to form a longitudinal validation study of normal aging and the MIS.

Exposure Study

To qualify for the exposure study a participant had to visit his SELECT site (which also had to agree to consent subjects for centralized follow-up) during the close out year, complete the final in-person screen, and consent to telephone follow-up. Consenters are telephoned from the PREADViSE coordinating center during their birth month and complete the MIS-T screen (19) as well as category and phonemic verbal fluency tests. If they fail the MIS-T, a TICS-M exam is given (20-22). A man who fails both procedures and who has a current medication list suggestive of cognitive impairment and/or past memory complaint is considered to be a suspected mild cognitive impairment in this study. He is then sent a packet of forms: an AD8 (23) (to evaluate changes in daily living skills), Geriatric Depression Scale (24) (to evaluate depression), a medical records release from, a reimbursement form for $300 to help cover the participant’s cost of a medical exam, and a form that requests the date of this exam and contact information for the doctor completing this workup. As with the RCT phase of the study, men with suspected or confirmed cases are encouraged to remain in the study.

Results

While this ancillary trial was open to all SELECT sites, only 30.0% participated in PREADViSE. This illustrates some reluctance from the cancer community to become involved in an area of research remote to their main interests, particularly when the site lacked personnel with expertise in