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Short Report

Impact of apolipoprotein E genotypes on vitamin E and memantine treatment outcomes in Alzheimer's disease

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Abstract

Introduction: Because apolipoprotein E (APOE) genotypes are known risk factors for Alzheimer's disease (AD), they have been measured in clinical trial participants to determine their effect on treatment outcome.

Methods: We determined APOE genotypes in a subset of subjects (N = 415) who participated in a randomized controlled trial of vitamin E and memantine in 613 veterans with mild-to-moderate AD.

Results: Similar to the primary study, substudy participants receiving vitamin E also had slower functional decline than those receiving placebo. Overall, there was no difference in the rate of functional decline between APOE ε4 allele carriers and noncarriers. A significant interaction was observed between treatment and the APOE genotype on AD progression: ε4 carriers declined faster than noncarriers in the vitamin E plus memantine treatment arm.

Discussion: APOE genotypes may modulate AD treatment response and should be included in the design of future randomized controlled trials.

Keywords: Alzheimer's disease; Vitamin E; Memantine; Apolipoprotein E genotypes; ApoE genotypes; APOE ε4 allele; Genotype-treatment interaction

1. Introduction

The Trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM-AD) was a double-blind, placebo-controlled randomized clinical trial involving 613 patients with Alzheimer's disease (AD) of mild-to-moderate severity, initiated in August 2007 and concluded in

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September 2012 at 14 Veterans Affairs (VAs) medical centers [1,2]. The trial's objective was to assess the effectiveness and safety of vitamin E, memantine, and the combination for treatment of functional decline in patients with mild-to-moderate AD. Details regarding the study design and the trial findings have been previously published [1,2].

A subset of the TEAM-AD trial participants (N = 415) also participated in a DNA Bank substudy that stored blood DNA for determination of apolipoprotein E (APOE) genotypes [2,3]. In this report, we examine the role of APOE genotypes on the effect of treatment in delaying the rate of functional decline of AD.

2. Methods

2.1. The TEAM-AD

The Department of VAs Cooperative Studies Program designed the TEAM-AD trial (Cooperative Studies Program No. 546) as a double-blind, placebo-controlled, parallel-group, randomized trial to assess the effectiveness of vitamin E, memantine, and the combination in delaying clinical progression in patients with AD currently taking an acetylcholinesterase inhibitor. Participants were veterans from 14 VA medical centers with a clinical diagnosis of either possible or probable AD [4] of mild or moderate severity as defined by a Mini–Mental State Examination total score between 12 and 26 inclusive [5]. Participants were randomly allocated to receive 2000 IU/d of vitamin E, 20 mg/d of memantine (Namenda), the combination, or placebo using 1:1:1:1 treatment allocation ratio. The duration of treatment ranged from 6 months to 4 years with participant follow-up every 6 months. The primary outcome measure was the Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) inventory [6]. The main finding of the TEAM-AD trial was that participants receiving vitamin E had slower functional decline than those receiving placebo as measured by the ADCS-ADL inventory [2].

2.2. The DNA Bank substudy

During or after screening for the main study, eligible patients were approached about participating in the DNA Bank substudy. All participants or their surrogates provided a separate written informed consent to participate in the DNA Bank substudy. The approach and consent rates were 81% and 84%, respectively.

Extracted DNA was stored at −80 C, and APOE genotyping was performed using TaqMan assays for SNPs rs7412 (C_904973_10 Thermo Fisher) and rs429358 (C_3084793_20 Thermo Fisher).

2.3. Statistical analysis

The DNA substudy data analysis used the primary outcome of the parent study, the ADCS-ADL inventory score, as its outcome measure. The effects of treatment and genotypes on the rate of AD function were analyzed by longitudinal repeated-measures mixed-effects models assuming missing at random, adjusted for medical center as a random effect, for baseline ADCS-ADL inventory scores, and potential confounding variables, such as age and self-reported ethnicity, specified in the footnote of each table and figure. All fitted models included time as a categorical predictor with an unstructured covariance matrix. Results are presented as least squares (LSs) means differences from baseline (with 95% confidence intervals [CIs]), representing the mean decline in function over the average follow-up period. *P* values are unadjusted for multiple comparisons. Data analyses were generated using SAS software, version 9.2 (SAS Institute, Cary, NC) and R, version 3.2.4 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org).

3. Results

The APOE ε2, ε3, and ε4 allele frequencies were 0.04, 0.66, and 0.30, respectively, with 50% of participants having at least one ε4 allele. The allele frequencies, genotype frequencies, and number of ε4 alleles did not differ among treatment groups (Supplementary Tables S1 and S2). Table 1 presents demographic and clinical characteristics of the substudy participants by APOE genotype. Compared with ε4 noncarriers, APOE ε4 carriers were significantly younger, less likely to be Hispanic, had a slightly higher mean AD Assessment Scale/Cognitive Subscale [7,8], and a slightly lower mean Charlson Risk Index score [9], which was a baseline measure predicting 10-year mortality based on 22 comorbid conditions.

An examination of the demographic and clinical characteristics of the substudy participants vs. those who did not consent to the substudy revealed that they were similar except for Hispanic ethnicity and mean Mini–Mental State Examination scores (Supplementary Table S3). Compared with those who did not participate in the DNA substudy, those who agreed to participate were more likely to be Hispanic (mainly due to high recruitment of Hispanics at the San Juan, Puerto Rico VA) and had slightly higher Mini–Mental State Examination scores.

An analysis of the main study's primary outcome in the substudy sample replicated the results of published finding in the main study (Supplementary Table S4) [2]. Over the mean follow-up time of 2.40 years (standard deviation (SD) = 1.23), the LS mean change (decline) from baseline in the ADCS-ADL inventory for the vitamin E treatment group was 3.19 units less than the decline in the placebo group (95% CI, 0.60–5.78); unadjusted $P = .016$). The annual rate of decline in ADLs was reduced by 22% with vitamin E (−4.94) compared with placebo (−6.30) or approximately 7.3 months over the follow-up period.

Table 1
Demographic and clinical characteristics of DNA substudy participants by APOE genotype

	ε4 noncarriers N = 209	ε4 carriers N = 206	*P*-value*
Age, mean (SD) [range], years	79.2 (6.9) [57–94]	77.7 (7.4) [53–92]	.0398
Male sex, No (%)	204 (97.6)	200 (97.1)	.7700
Race, no (%)			.8784
White	183 (87.6)	183 (88.8)	
Black	25 (12.0)	22 (10.7)	
Other	1 (0.5)	1 (0.5)	
Ethnicity			.0221
Hispanic or Latino, no (%)	37 (17.7)	20 (9.7)	
Education, no (%)			.8590
< High school graduate	47 (22.4)	51 (24.8)	
High school graduate	71 (34.0)	69 (33.5)	
Some college	48 (23.0)	41 (19.9)	
College graduate or advanced degree	43 (20.6)	45 (21.8)	
Charlson Risk Index score, mean (SD) median [range][†]	2.6 (1.6) 2 [1–9]	2.3 (1.8) 2 [1–14]	.0075
Comorbidity Disease index domains, no (%)[‡]			.0914
≤1	87 (41.6)	100 (48.5)	
2	52 (24.9)	57 (27.7)	
≥3	70 (33.5)	49 (23.8)	
AChEI, no (%)			.4908
Donepezil	135 (64.6)	133 (64.6)	
Galantamine	70 (33.5)	65 (31.6)	
Rivastigmine	4 (1.9)	8 (3.9)	
Time from AChEI start to randomization			.3356
≤12 wk	58 (27.8)	67 (32.5)	
>12 wk	151 (72.3)	139 (67.5)	
ADCS-ADL inventory score, mean (SD) median [range][§]	57.8 (13.1) 60 [21–78]	56.9 (14.3) 61 [15–78]	.7769
MMSE score, mean (SD) median [range][¶]	21.6 (3.3) 22 [13–26]	21.1 (3.8) 22 [12–26]	.0789
ADAS-cog score, mean (SD) median [range][#]	17.4 (7.7) 16 [2–48]	19.5 (8.7) 18 [4–56]	.0076
NPI score, median [range]**	8 [0–62]	9 [0–81]	.5185
CAS time, median [range], h[††]	2.9 [0–59]	3.0 [0–144]	.4220

Abbreviations: AChEI, acetylcholinesterase inhibitor; ADAS-cog, Alzheimer Disease Assessment Scale–Cognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study/Activities of Daily Living; CAS, Caregiver Activity Survey; MMSE, Mini–Mental State Examination; NPI, Neuropsychiatric Inventory; APOE, apolipoprotein E; SD, standard deviation.

*For continuous variables, Kruskal-Wallis test *P*-values are reported; for categorical variables, Fisher's exact test *P*-values are reported.

[†]Charlson Risk Index score predicts 10-year mortality based on 22 comorbid conditions, each assigned 1, 2, 3, or 6, depending on risk of dying associated with the condition [7].

[‡]Comorbidity Disease Index domains include cardiac, respiratory, neurologic, musculoskeletal, general (mental or emotional problems and sleep or pain disorders), cancer, diabetes, and visual problems. The domain scores are totaled to create an overall comorbidity score (≤1, 2, or ≥3 domains).

[§]ADCS-ADL Inventory Score: range, 0–78; higher scores = better functioning [6].

[¶]MMSE score: range, 0–30; higher scores = better functioning [5].

[#]ADAS-cog score assesses cognitive function in the areas of memory, language, and praxis functions; range, 0–70: higher scores = worse functioning [8,9].

**NPI score assesses frequency and severity of psychological and behavioral problems in patients with dementia; range, 0–144; higher scores = more frequent and/or severe behavioral problems [10].

[††]CAS time measures caregiver time in caring for patients with dementia, summing total hours spent in a day on 6 caregiving tasks; range, 0–144 hours: higher scores = more time spent on caregiving [11].

With all randomized groups combined, there was no significant difference in functional decline between participants with no ε4 alleles and those with one or more ε4 alleles (Supplementary Table S5).

A significant interaction effect of treatment and the number of ε4 alleles on AD functional decline was observed (Table 2, Supplementary Table S6, Supplementary Figures S1 and S2). Comparing ε4 noncarriers in the three active treatment groups to placebo, the mean (95% CI) decline from baseline in ADCS-ADL inventory was 3.72 units (0.08–7.26) less in the vitamin E group, 2.93 units (−0.67 to 6.53) less in the memantine group, and 4.60 units (1.16–8.04) less in the combination group over the mean (standard deviation) follow-up time of 2.40 (1.23) years (Table 2, Supplementary Figure S2). In ε4 carriers, only participants taking vitamin E had slower decline compared with placebo:

Table 2
Mean changes in ADCS-ADL Inventory* in the substudy participants over the mean (SD) follow-up time of 2.40 (1.23) years as compared with baseline

Panel A: ε4 noncarriers				
ADCS-ADL Inventory	Vitamin E N = 47	Memantine N = 48	Vitamin E + memantine N = 59	Placebo N = 55
Baseline score, mean (SD)	55.38 (14.06)	59.71 (13.25)	58.47 (11.55)	57.55 (13.55)
Least squares mean (95% CI) change from baseline	−11.56 (−14.8, −8.3)	−12.36 (−15.6, −9.1)	−10.68 (−13.7, −7.6)	−15.28 (−18.4, −12.1)
Mean (95% CI) annual rate of functional decline†	4.82 (3.5, 6.2)	5.15 (3.8, 6.5)	4.45 (3.2, 5.7)	6.37 (5.1, 7.7)
Mean (95% CI) difference compared with placebo	3.72 (0.08, 7.36)	2.93 (−0.67, 6.53)	4.60 (1.16, 8.04)	Reference
Unadjusted *P*-value‡	.0450	.1110	.0089	Reference
Panel B: ε4 carriers				
ADCS-ADL inventory	Vitamin E N = 49	Memantine N = 57	Vitamin E + Memantine N = 52	Placebo N = 48
Baseline score, mean (SD)	59.14 (14.76)	56.05 (14.35)	55.92 (15.19)	56.73 (12.92)
Least squares mean (95% CI) change from baseline	−11.82 (−14.9, −8.7)	−14.67 (−17.6, −11.7)	−16.09 (−19.2, −13.0)	−15.22 (−18.4, −12.1)
Mean (95% CI) annual rate of functional decline†	4.93 (3.6, 6.2)	6.11 (4.9, 7.4)	6.70 (5.4, 8.0)	6.30 (5.0, 7.7)
Mean (95% CI) difference compared with placebo	3.39 (−0.21, 7.02)	0.55 (−2.94, 4.04)	−0.86 (−4.46, 2.73)	Reference
Unadjusted *P*-value‡	.0653	.7565	.6378	Reference

Abbreviations: ADCS-ADL, Alzheimer's Disease Cooperative Study/Activities of Daily Living; CI, confidence interval; SD, standard deviation.
*Based on longitudinal repeated-measures mixed-effects model, adjusted for medical center as a random effect and for baseline ADCS-ADL inventory score.
†Annual rate of decline is calculated by dividing the LS means change by the average follow-up time.
‡*P*-value is unadjusted for multiple comparisons.

mean (95% CI) difference of 3.39 (−0.21 to 7.02) compared with placebo.

In the vitamin E, memantine, and the placebo arms, there was no difference in functional decline between ε4 carriers and noncarriers (Supplementary Table S6, Supplementary Figure S1). However, in the combination treatment arm, ε4 carriers had significantly slower functional decline than noncarriers as measured by the ADCS-ADL inventory: the LS mean change (decline) from baseline for ε4 noncarriers was 5.90 units less than the decline in ε4 carriers (95% CI, 2.52, 9.29).

4. Discussion

This study examined the effects of APOE genotypes on functional decline in a subset of subjects who participated in the TEAM-AD study. The results from this substudy are consistent with results in the main study in that participants receiving vitamin E had a slower decline compared with the placebo group as measured by the ADCS-ADL.

The ε4 allele frequency (0.30) in this substudy is typical of AD case groups [12,13]. In addition, the younger age of the ε4-positive group compared with the non-ε4 group is consistent with the age-at-onset effect typically observed in other studies [14,15]. Although the main effect of APOE genotype on the rate of functional decline was not significant, the analyses of the relationship of APOE ε4 allele and treatment response showed an interaction effect, with ε4 carriers declining faster compared with noncarriers in the combination treatment arm, even after correction for confounding variables, for example, age, ethnicity, Charlson Index Score, and ADAS-cog. There was no significant difference between ε4 carriers and noncarriers in the other three arms. The relationship between APOE genotypes and rate of decline in other studies is unclear with some showing no relationship and others showing that subjects with ε4 alleles decline faster than those without [16].

The genetics of late-onset AD is polygenic, and over 25 loci affecting risk are known. However, APOE has been shown to have the largest effect size of any AD genetic risk factor. The APOE ε4 allele increases the risk of AD by two-fold to three-fold in heterozygous ε4 carriers and 12-fold in homozygous ε4 [17]. For other AD genetic risk variants, odds ratios are less than 3.0 with most between 1.1 and 1.4 [18]. This study was not powered to determine if these other variants influence response to vitamin E or memantine; however, APOE genotypes may be useful in determining both subject selection and predicting treatment response in future AD pharmacologic trials.

The mechanism by which APOE genotypes may influence response to vitamin E is unclear, in part because how APOE genotypes influence AD is not known. One theory is that APOE may influence AD risk though its established role in cholesterol transport [19,20]. Certainly, because vitamin E and cholesterol share mechanisms of delivery to cells via LDL particles, vitamin E-APOE genotype interactions could involve these common uptake pathways. However, another hypothesis, not linked to vitamin E, is that APOE binds and clears amyloid β, the toxic peptide central to AD pathogenesis [17,20]. A biological explanation of the genotype-treatment interaction demonstrated here awaits further work on the role of APOE in AD pathogenesis.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2018.06.001.

RESEARCH IN CONTEXT

1. Systematic review: The authors searched the literature using PubMed for specific studies examining the relationship between apolipoprotein E (APOE) genotypes and Alzheimer's disease (AD) progression and treatment.
2. Interpretation: We assessed the associations between APOE genotypes, specifically number of ε4 alleles, and clinical progression of AD as measured by the Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory and effects of vitamin E and memantine treatments. Overall, there was no difference in the rate of functional decline between APOE ε4 allele carriers and noncarriers. A significant interaction effect was observed between treatment and the APOE genotype on AD progression: ε4 carriers declined faster than noncarriers in the vitamin E plus memantine treatment arm. This may mean that the effect of these and other AD therapies are lessened depending on number of ε4 alleles.
3. Future directions: Additional research is needed to confirm the weaker treatment effect of vitamin E plus memantine in patients with AD with ε4 alleles and to explore possible basic mechanisms underlying this observation.

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Appendix 1

The following persons participated in the DNA Bank substudy. VA TEAM-AD Study: Planning Committee: M. Dysken (Study Chair), S. Asthana, P. Guarino, J. Hanlon, M. Kunik, P. Lavori, P. Peduzzi, E. Perry,M. Sano, G. Schellenberg, T. Sunderland, G. Vatassery (deceased), J. Vertrees, and L. Volicer. Executive Committee: M. Dysken (Chair), S. Asthana, P. Guarino, M. Llorente, S. Love, M. Pallaki, M. Sano, G. Schellenberg, G. Vatassery (deceased), and J. Vertrees. Data Monitoring Committee: K. Kieburtz (Chair), C. Kawas, E. Lonn (resigned), P. Rabins, J. Rochon, D. Sultzer, and R. Thomas. VA Cooperative Studies Program Human Rights Committee, West Haven, Connecticut: R. Marottoli (Chair), H. Allore, D. Beckwith, W. Farrell, R. Feldman, R. Mehta, J. Neiderman, E. Perry, S. Kasl, and M. Zeman. VA Site Investigators and Coordinators: Ann Arbor, Michigan: J. Heidebrink, R. S. Turner, N. Barbas, C. Bloehm, J. Lord, K. Belanger, N. Ricci, C. Nwankwo, C. Fletcher; Baltimore, Maryland: D. Loreck, L. Katzel, K. Anderson, G. Kavanagh, S. Carney, A. Loreck. (Bay Pines, Florida) A. Cruz, S. Reddy, N. Purohit, R. Tamayo, K. Monnell, S. Huda, S. Zachariah, W.C. McCarthy; Boston, Massachusetts: N. Kowall, M. Chopra, B. Seltzer (deceased), K. Kolbe; Charleston, South Carolina: J. Mintzer, O. Brawman-Mintzer, A. Senseney, D. Courtney, M. Stuckey, S. Russell, J. A. Sweeney; Cleveland, Ohio: M. Pallaki, P. Chen, T. Hornick, T. Dolinar, L. Abood, A. Coulter, S. Truax, D. Davis; Dallas, Texas; G. Trapp, R. Bakshi, L. Moody, N. Flye, D. Turner-Knight; Iowa City, Iowa: C. Turvey, C. Woodman, A. Ray, K. Ekstam Smith, N. Suiter; Madison, Wisconsin: S. Asthana, C. Gleason, S. Barczi, C. Carlsson, N. Lane, M. Wroblewski, Z. Zugin, J. J. Fruehling; Miami, Florida: J. Malphurs, M. Llorente, F. Adan, S. Prieto, M. Horvath, D. Santiago, G. Athappilly, A. Cortes, A. Vazquez, R. Dreize, F. Ostovary, E. Palaois, M. Oliveira, J. Pino, L. Claude; Minneapolis, Minnesota: J. McCarten, H. Fink, C. Erickson, L. Becker-Grandle; Salisbury, North Carolina: K. Monnell, K. Gordon, K. Phillips, D. Eknoyan; San Juan, Puerto Rico: A. Vidal-Cardona, L. Arroyo, A. Melendez, L. Santiago, B. Padilla; Seattle, Washington: S. Craft, J. Breitner, S. Thielke, K. Enstrom, J. Tidwell, R. Bridgan, K. Bowton, and D. Dahl. Study Chair's Office, VA Health Care System, Minneapolis: M. Dysken (Study Chair), S. Love, and J. Tomaska. Central Laboratory, VA Health Care System, Minneapolis: G. Vatassery (deceased), Y. Segal, E. Smith, and H. Quach. VA Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven: P. Guarino (Director, Study Biostatistician), M. Antonelli, E. Jobes, C. Joncas, S. Joyner, K. Kirkwood, P. Peduzzi, M. Perry, E. Petrokaitis, J. Russo, J. Scholl, S. Yang, and S. Zellner. VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, New Mexico: M. Sather (Director), J. Vertrees (Study Clinical Research Pharmacist), S. Campbell, D. Conner, E. Copeland, A. Davis S. Jenkins, and B. Matura. VA Cooperative Studies Program Site Monitoring, Auditing and Review Team, Albuquerque: C. Haakenson and D. Krueger. VA Cooperative Studies Program Central Biorepository (MAVERIC), VA Healthcare System, Boston: M. Brophy (Director), D. Humphries, and D. Govan. VA Cooperative Studies Program DNA Bank Coordinating Center, VAMC Palo Alto, CA: I. Belitskaya-Lévy, P. Lavori, S. Au, J. Cockroft, S. Bobra, A. Baylosis, V. Krishnan, and R. Dodson. VA Office of Research and Development, Clinical Science Research and Development, Washington, DC: T. O'Leary (Director, Deputy Chief Research and Development Officer), S. Muralidhar (Director, Million Veteran Program), and G. Huang (Deputy Director, Cooperative Studies Program).