Original Research Article

Role of APOE and Age at Enrollment in the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT)

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Key Words

Prevention · Clinical trial · Alzheimer's disease · Apolipoprotein E · Age

Abstract

Background: The Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) tested whether non-steroidal anti-inflammatory drugs (NSAIDs) can prevent Alzheimer's disease (AD). The results were null. We analyzed ADAPT data to examine if the effects of NSAIDs on AD risk differed depending upon *APOE* genotype or age as has been suggested by previous observational studies. **Methods:** ADAPT randomized 2,528 cognitively intact older adults to either celecoxib, naproxen sodium or placebo; 2,388 participants provided blood samples for *APOE* genotyping. Proportional hazards regression was used to estimate the effects of naproxen or celecoxib versus placebo on incident AD by age at enrollment and *APOE* genotype. **Results:** The proportion of subjects providing a biological sample did not differ between the treatment groups. In models of AD risk, none of the tests for 2-way interactions between either NSAID and age or *APOE* genotype were significant (p > 0.05). **Conclusions:** The data did not support the hypothesis that the association between NSAIDs and AD risk differed by age or *APOE* genotype.

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Introduction

Previous epidemiologic studies have found that non-steroidal anti-inflammatory drugs (NSAIDs) are associated with reduced risk of Alzheimer's disease (AD) [for a review, see 1]. Several of these studies have suggested the risk reduction may be greater among certain subgroups. In one study, NSAIDs were associated with reduced AD risk only among those with at least one high-risk ε4 allele [2]. Several other studies noted similar albeit non-significant subgroup differences by *APOE* genotype [3–5]. Two other observational studies reported that the association between NSAIDs and reduced AD risk was greatest among the youngest old and diminished with increasing age [2, 6].

The Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) was designed to evaluate whether the nonselective NSAID naproxen sodium (Aleve®, Bayer) or the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib (Celebrex®, Pfizer) prevent AD onset among cognitively intact elderly with a family history of AD. Primary results reported from the trial did not support the hypothesis that NSAIDs prevent AD or age-related cognitive decline [7, 8]. This report describes analyses of ADAPT data to determine if the effect of the NSAIDs on AD incidence differed by *APOE* genotype or age at enrollment in the trial.

Methods

Design Overview

ADAPT was a randomized, placebo-controlled, primary prevention trial sponsored by the National Institute on Aging. Participants were assigned to the following parallel treatment groups in a 1:1:1.5 ratio: (a) naproxen (220 mg b.i.d.); (b) celecoxib (200 mg b.i.d.), or (c) placebo. Participants and personnel at the clinical sites were masked to treatment assignment using a double-placebo design [9]. The study protocol was reviewed and approved by all relevant institutional review boards.

ADAPT participants were recruited primarily through mailings to Medicare beneficiaries in areas surrounding the trial's six field sites in the United States (Baltimore, Md.; Boston, Mass.; Rochester, N.Y.; Seattle, Wash.; Sun City, Ariz.; Tampa, Fla.). Participants were aged 70 years or older, with a history of at least one first-degree relative with Alzheimer-like dementia. Participants underwent cognitive screening before enrollment to exclude those with dementia or other cognitive disorders.

Participants were enrolled from March 2001 to December 2004 and screened annually by an in-person cognitive assessment battery. In December 2004, enrollment and treatment administration were suspended earlier than planned following the announcement from the Adenoma Prevention with Celecoxib (APC) trial that the dose of celecoxib used in ADAPT produced substantially increased risks of cardiovascular death, myocardial infarction, and related events. The rationale for suspending both treatments in ADAPT has been fully discussed [10]. A subsequent analysis of ADAPT data did not show the same level of risk for celecoxib as those of the APC trial [11]. The follow-up of patients enrolled in ADAPT continued until a common closing date in February 2007. A detailed description of the ADAPT design and methods has been published [12].

Outcome Assessment

Participants with possible cognitive syndromes were identified using cognitive assessment batteries or via referral from study clinicians and were invited to return to a study clinic for a dementia evaluation visit. A description of the battery of tests and procedures used in ADAPT for cognitive assessments and dementia evaluations has been published [7].

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The laboratory, neuroimaging, and cognitive battery results from the annual study visits and the dementia evaluation visit were reviewed by a diagnostic expert panel including the examining clinicians, other ADAPT physicians, and senior site neuropsychologists. When appropriate, the panel assigned diagnoses of dementia using the Diagnostic and Statistical Manual of Mental Disorders-IV criteria [13] and of Alzheimer's dementia using the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria [14].

APOE Genotyping

At enrollment, 5–7 ml of blood was collected from participants who consented to DNA banking. Whole-blood specimens were shipped at room temperature to the Johns Hopkins University Genetic Resources CORE Facility in Baltimore, Md., and DNA was extracted for genetic investigations. APOE genotyping was carried out using standard protocols with the NanoChip® Molecular Biology Workstation (Nanogen) platform.

Data Analysis

Pearson χ^2 tests were used to compare participants who did and did not provide specimens for DNA banking. Naproxen and celecoxib were each compared with placebo. We evaluated time-to-occurrence of AD using the principle of intention-to-treat (ITT) with Cox proportional hazards regression models [15] excluding participants with no follow-up data. For those participants without an AD event, person-time was censored after the participants' last completed cognitive assessment. The event date for those participants with a diagnosis of AD was taken as the date of the relevant dementia evaluation visit. To test for different treatment effects by age and APOE genotype, we separately examined models with 2-way interactions between treatment and age category (dichotomized at the median baseline age; age <74 years vs. age ≥74 years) or treatment and APOE genotype (dichotomized at one or more APOE ε4 alleles vs. no ε4 alleles). Models were adjusted for field site and 5-year age group (for models not including the dichotomized age variable). The resulting hazard ratios (HRs) were estimated with 95% CIs and Wald p values using the PHREG procedure in SAS (SAS/STAT® software, version 9.2 of the SAS System for Windows; Copyright© 2002–2008 SAS Institute Inc., Cary, N.C., USA).

Results

The flow of participants through randomization and follow-up and the demographic characteristics of the entire randomized cohort have been shown in previous publications [7, 8, 11]. Briefly, 2,528 participants were randomized (placebo: 1,083; celecoxib: 726; naproxen: 719), and 2,071 participants had at least one follow-up visit (placebo: 895; celecoxib: 588; naproxen: 588).

A total of 2,388 participants provided DNA specimens for APOE genotyping. The proportion of participants providing specimens did not differ appreciably between the treatment groups. The proportion of participants not providing specimens was slightly higher for women than men (6.8 vs. 4.5%; $\chi^2 = 6.6$; p = 0.01) and varied significantly by race (5.3% White, 18.9% African-American, 0% Hispanic, 13.6% other; $\chi^2 = 16.7$, p < 0.01) and marital status (4.5% married, 9.5% widowed, 15.4% separated, 6.4% divorced, 3.1% never married; $\chi^2 = 21.6$; p < 0.01). The proportion of participants not providing specimens also differed by clinic (5.0% Baltimore, 8.7% Boston, 4.4% Rochester, 11.0% Seattle, 1.1% Sun City, 3.3% Tampa; $\chi^2 = 58.1$; p < 0.01).

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Table 1. Baseline characteristics of ADAPT participants providing DNA

	Total	Placebo	Celecoxib	Naproxen sodium
Participants	2,528	1,083	726	719
Provided DNA, n (%)	2,388 (94.5)	1,023 (94.5)	686 (94.5)	679 (94.4)
Age group, n (%)				
70–74 years	1,325 (55.5)	562 (54.9)	385 (56.1)	378 (55.7)
75–79 years	754 (31.6)	324 (31.7)	214 (31.2)	216 (31.8)
80–84 years	269 (11.3)	120 (11.7)	76 (11.1)	73 (10.8)
≥85 years	40 (1.7)	17 (1.7)	11 (1.6)	12 (1.8)
Gender, n (%)				
Male	1,307 (54.7)	573 (56.0)	365 (53.2)	369 (54.3)
Female	1,081 (45.3)	450 (44.0)	321 (46.8)	310 (45.7)
Race/ethnic origin, n (%)				
White	2,321 (97.2)	998 (97.6)	661 (96.4)	662 (97.5)
African-American	30 (1.3)	9 (0.9)	11 (1.6)	10.0 (1.5)
Hispanic	18 (0.8)	6 (0.6)	10 (1.5)	2 (0.3)
Other	16 (0.7)	9 (0.9)	3 (0.4)	4 (0.6)
Refused	3 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Education, n (%)				
Less than high school	99 (4.2)	37 (3.6)	28 (4.1)	34 (5.0)
High school graduate	475 (19.9)	212 (20.7)	144 (21.0)	119 (17.5)
Some college	655 (27.4)	272 (26.6)	191 (27.8)	192 (28.3)
College degree	460 (19.3)	215 (21.0)	130 (19.0)	115 (16.9)
Postgraduate education	699 (29.3)	287 (28.1)	193 (28.1)	219 (32.3)
Marital status, n (%)				
Married	1,736 (72.7)	734 (71.8)	486 (70.8)	516 (76.0)
Widowed	417 (17.5)	183 (17.9)	129 (18.8)	105 (15.5)
Separated	11 (0.5)	7 (0.7)	3 (0.4)	1 (0.1)
Divorced	160 (6.7)	73 (7.1)	49 (7.1)	38 (5.6)
Never married	63 (2.6)	25 (2.4)	19 (2.8)	19 (2.8)
Not reported	1 (0.0)	1 (0.1)	0	0
APOE alleles, n (%)				
ε2/ε2	7 (0.3)	3 (0.3)	3 (0.4)	1 (0.1)
ε2/ε3	253 (10.6)	114 (11.1)	74 (10.8)	65 (9.6)
ε2/ε4	82 (3.4)	34 (3.3)	23 (3.4)	25 (3.7)
ε3/ε3	1,286 (53.9)	549 (53.7)	353 (51.5)	384 (56.6)
ε3/ε4	695 (29.1)	296 (28.9)	216 (31.5)	183 (27.0)
ε4/ε4	65 (2.7)	27 (2.6)	17 (2.5)	21 (3.1)

Table 1 shows the demographic characteristics of the 2,388 participants who provided specimens overall and by treatment group. The median age at randomization was 74 years; slightly more males than females were included, and more than 97% of the participants were white. Approximately one-third of the participants had at least one *APOE* ε4 allele; only 3% had homozygous ε4. More than half of the participants were homozygous for ε3.

The incidence of AD was higher among participants with one (HR = 2.4, 95% CI: 1.3–4.4, p < 0.01) or two (HR = 6.2, 95% CI: 2.3–16.6, p < 0.01) *APOE* ε4 alleles as compared to those with no ε4 alleles. The incidence of AD was higher in participants older than 74 years compared to those younger than 74 years, although the confidence interval for the hazard ratio included one (HR = 1.3, 95% CI: 0.7–2.3, p = 0.41).

The 2-way tests for interaction did not provide support for the hypothesis that the treatment effects differed by age (celecoxib-by-age interaction p value = 0.66, naproxen-by-age interaction p value = 0.72) or by *APOE* genotype (celecoxib-by-ε4 status interaction p

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Table 2. Incidence of AD by treatment group, *APOE* alleles and age

	Placebo		Celecoxib			Naproxen		
	rate/100 PY	x/N	rate/100 PY	x/N	HR (95% CI)	rate/100 PY	x/N	HR (95% CI)
Model 1								
Presence of APOE *ε*4 alleles								
0 APOE *ε*4 alleles	0.6	12/666	0.6	8/430	0.93 (0.38–2.30)	0.5	7/450	0.80 (0.31–2.06)
1–2 APOE *ε*4 alleles	1.5	17/357	1.7	14/256	1.14 (0.56–2.33)	1.3	9/229	0.91 (0.41–2.05)
Missing APOE data		1/60		2/40			2/40	
Model 2								
Baseline age								
<74 years	0.7	12/498	0.7	7/320	0.97 (0.38–2.47)	0.8	8/328	1.00 (0.41–2.46)
≥74 years	1.0	18/585	1.3	17/406	1.25 (0.64–2.43)	0.8	10/391	0.82 (0.38–1.78)

x/N = Number of events divided by the number of persons at risk; PY = cumulative person-years of follow-up; PYs can be calculated as the number of events/(rate/100). Event is defined as possible or probable AD based on consensus conference. Hazard ratios and 95% confidence intervals (NSAID vs. placebo) were calculated using Cox proportional hazards regression. Time to event is from randomization to the date of the associated dementia evaluation. Time to censor is from randomization to the most recent cognitive assessment. Models included adjustment for stratification variables of field site (both models) and 5-year age group (model 1 only).

value = 0.82, naproxen-by-*ε*4 status interaction p value = 0.90). The HRs for each NSAID versus placebo are shown in table 2 stratified by the presence of *APOE ε*4 alleles (model 1) and age category (model 2).

Discussion

ADAPT was carried out to test the hypothesis that NSAIDs prevent the onset of AD. The primary results did not provide any support for this hypothesis. The source of the discrepant results between the randomized trial and previous observational studies has been the focus of much debate [1]. Motivated by findings of several previous observational studies that the effects of NSAIDs may be greater among the youngest old or those with one or more *APOE ε*4 allele, we analyzed ADAPT data to test for subgroup differences by age or *APOE* genotype that might explain the discrepancies between the observational and randomized studies. We found no evidence for such subgroup differences.

This is the first randomized study of NSAIDs and AD to test for subgroup differences by age or *APOE* genotype. Randomized trials are considered the gold standard for establishing causal relationships in epidemiology. However, the current study was not designed to test for treatment by genotype or age interactions and may not have had sufficient sample size to rule out important differences in treatment effects by age or *APOE* genotype. For instance, the estimated hazard ratio for naproxen versus placebo in the subgroup with *APOE ε*4 alleles was close to 1.0 (i.e. HR = 0.91), but the confidence interval contained values that would probably be regarded as clinically significant, i.e. potentially a 60% reduction in AD incidence. Similarly for celecoxib versus placebo in those with *ε*4 alleles, the wide confidence intervals meant that we are unable to rule out a 40% reduction in AD incidence. The current findings do argue, however, against subgroup effects on AD incidence of these magnitudes or greater.

Funding

Appendix 1: ADAPT Research Group

Clinical Centers

Boston University School of Medicine, Boston, Mass.: Robert Green, MD (director); Sanford Auerbach, MD (associate director); Robert Stern, PhD (neuropsychologist); Patricia Boyle, PhD (previous neuropsychologist); Dawn Cisewski, PhD (previous neuropsychologist); Jane Mwicigi, MD (coordinator); Mary-Tara Roth, RN, MSN (previous coordinator); Lorraine Baldwin; Margaret Brickley, RN, NP; Patrick Compton, RN; Debra Hanna, RN; Sylvia Lambrechts; Janet Nafissi, MSN, APRN; Andrea Packard, MD, PhD; Mayuri Thakuria, MD.

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The Roskamp Institute Memory Clinic, Tampa, Fla.: Michael Mullan, MD, PhD (director); Cheryl Luis, PhD (associate director, neuropsychologist); Timothy Crowell, PsyD (previous associate director, neuropsychologist); Julia Parrish (coordinator); Theavy Chea; Scott Creamer; Melody Brooks Jayne, MD; Antoinette Oliver; Summer Price; Joseph Zolton.

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Resource Centers

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Office of Chair: Veteran Affairs Puget Sound Health Care System, Seattle, Wash.: John Breitner, MD (director); Jane Anau (coordinator); Melissa Montero (previous coordinator); Janette Negele (previous coordinator); Elizabeth Aigbe; Jill Dorje; Brenna Cholerton, PhD.

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Project Office: National Institute on Aging, Bethesda, Md.: Neil Buckholtz, PhD (project officer); Laurie Ryan, PhD (project officer); Susan Molchan, MD (previous project officer).

Steering Committee

Voting: Denis Evans (chair since March 2005, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Ill.; Curtis Meinert, through February 2005); John Breitner; Jason Brandt; Neil Buckholtz; Suzanne Craft; Robert Green; M. Saleem Ismail (since December 2005); Constantine Lyketsos; Barbara Martin; Curtis Meinert; Susan Molchan; Michael Mullan; Steven Piantadosi; Marwan Sabbagh; Pierre Tariot (through October 2005).

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Treatment Effects Monitoring Committee

Voting: C. Morton Hawkins, PhD (chair since December 2002, Frontier Science and Technology Research Foundation, Madison, Wisc.; Donald Berry, PhD, through April 2002); Bernard Carroll, MBBS, PhD, Pacific Behavioral Research Foundation, Carmel, Calif.; Ronald Petersen, MD, PhD, Mayo Clinic, Rochester, Minn.; Bruce Psaty, MD, PhD, University of Washington, Seattle, Wash.; Thomas Schnitzer, MD, PhD, Northwestern University, Chicago, Ill.; Dallas High, PhD (through June 2004).

Non-voting: Neil Buckholtz; Denis Evans; Curtis Meinert.

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